OVERSIGHT OF THE DRUG DEVELOPMENT PROGRAM OF THE NATIONAL CANCER INSTITUTE, 1982

HEARING

BEFORE THE

SUBCOMMITTEE ON INVESTIGATIONS AND GENERAL OVERSIGHT

OF THE

COMMITTEE ON LABOR AND HUMAN RESOURCES UNITED STATES SENATE

NINETY-SEVENTH CONGRESS

SECOND SESSION

ON

EXAMINATION OF EFFECTIVE ALTERNATIVES TOWARD CORRECTING DEFICIENCIES IN THE USE OF EXPERIMENTAL DRUGS ON CANCER PATIENTS

MARCH 5, 1982

Printed for the use of the Committee on Labor and Human Resources

U.S. GOVERNMENT PRINTING OFFICE
93-889 O
WASHINGTON : 1982

541-49

COMMITTEE ON LABOR AND HUMAN RESOURCES

ORRIN G. HATCH, Utah, *Chairman*

ROBERT T. STAFFORD, Vermont
DAN QUAYLE, Indiana
PAULA HAWKINS, Florida
DON NICKLES, Oklahoma
LOWELL P. WEICKER, Jr., Connecticut
GORDON J. HUMPHREY, New Hampshire
JEREMIAH DENTON, Alabama
JOHN P. EAST, North Carolina

EDWARD M. KENNEDY, Massachusetts
JENNINGS RANDOLPH, West Virginia
HARRISON A. WILLIAMS, Jr., New Jersey
CLAIBORNE PELL, Rhode Island
THOMAS F. EAGLETON, Missouri
DONALD W. RIEGLE, Jr., Michigan
HOWARD M. METZENBAUM, Ohio

George W. Pritts, Jr., *Chief Counsel*
Renn M. Patch, *Staff Director and General Counsel*
Lawrence C. Horowitz, M.D., *Minority Staff Director*

Subcommittee on Investigations and General Oversight

PAULA HAWKINS, Florida, *Chairman*

GORDON J. HUMPHREY, New Hampshire
ORRIN G. HATCH, Utah,
(Ex Officio)

EDWARD M. KENNEDY, Massachusetts
(Ex Officio)

Jay C. Howell, *Chief Counsel*
Walter Sheridan, *Minority Professional Staff Member*

CONTENTS

CHRONOLOGICAL LIST OF WITNESSES

Friday, March 5, 1982

Page

Brandt, Edward N., Jr., M.D., Assistant Secretary for Health, Department of Health and Human Services, accompanied by Lowell T. Harmison, Ph. D., Chairman, Task Force, Science Adviser, Office of the Assistant Secretary of Health, U.S. Public Health Service 3

Prepared statement 7

ADDITIONAL INFORMATION

Articles, publications, etc.:

Anticancer drugs: National Cancer Institute's development and the Food and Drug Administration's regulation, summary report on, from the task force on NCI-FDA Investigational New Drugs Task Force:

Volume I, January 8, 1982 (with attachments) 31

Volume II, January 28, 1982 (with attachments) 101

OVERSIGHT OF THE DRUG DEVELOPMENT PROGRAM OF THE NATIONAL CANCER INSTITUTE, 1982

FRIDAY, MARCH 5, 1982

U.S. Senate,
Committee on Labor and Human Resources,
Subcommittee on Investigations and General Oversight,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10:30 a.m., in room 4232, Dirksen Senate Office Building, Senator Paula Hawkins (chairman of the subcommittee) presiding.

Present: Senator Hawkins.

Staff present: Jay Howell and Terri Parker, counsels; Tim Jenkins and Lisa Demetree, staff investigations; and Westley Clark, minority counsel.

Opening Statement of Senator Hawkins

Senator **Hawkins**. I will call this hearing to order today.

We are here today to again examine the drug development program of the National Cancer Institute's and its regulation by the Food and Drug Administration. This subcommittee has met on three previous occasions to consider some very serious program deficiences which have plagued the use of experimental chemotherapeutic drugs.

Again, let me emphasize that I remain convinced that the NCI's drug development program is needed and must be continued. Through constructive solutions to the program deficiencies at NCI we can assure the thousands of cancer patients now in treatment that they should continue to trust in the care of their doctors.

When this subcommittee initiated the inquiry into the National Cancer Institute our purposes were to: First, identify program deficiencies and problem areas; second, to make them known to the appropriate managers and directors; third, to put these deficiencies and problems in proper perspective; and fourth, to encourage and effect their repair.

The purpose of our meeting today is to specifically address the fourth aspect of our mission—to encourage and effect their repair.

During this subcommittee's cancer hearings in 1981, we disclosed serious problems in management at the National Cancer Institute. Evidence before this subcommittee convinced me of the critical need for adequate monitoring of the National Cancer Institute's clinical trials. There is lack of accountability in the use of NCI's drugs, a shortage of resources to adequately analyze data and the results of clinical trials, and improper delays in the submission of the appropriate data to the Food and Drug Administration. Of utmost concern to me is the situation in which a patient's adverse reaction to an experimental drug is not promptly reported to the National Cancer Institute nor relayed by the NCI to the Food and Drug Administration.

The threshold question was and still remains one of patient safety. Approximately 37,000 patients will receive experimental chemotherapy treatment this year. I believe the evidence the subcommittee will hear today will take significant strides toward a realistic solution to these problems.

In June 1981, I wrote to Health and Human Services Secretary, Richard Schweiker, to inform him of the specific findings of the subcommittee and to seek his help in pursuing a constructive solution. Secretary Schweiker responded by appointing a special task force under the direction of the Assistant Secretary for Health, Dr. Edward N. Brandt, Jr. The objective of the task force, to review and evaluate the NCI-FDA programs.

Today we will hear from Dr. Brandt and his colleagues on the task force as they report their findings. I am particularly encouraged and impressed with the work of this task force. With the presentation of this report, I believe that we are finally on the road to finding workable solutions to the problems we have identified in the past.

Much of the task force's report substantiates the existence of specific program deficiencies within the developmental drug program. The task force's examination of two particular substances, Methyl-CCNU and 5 Methyl-THHF, convinced the members of the task force that the problems encountered in these cases are not isolated. The task force concluded that the National Cancer Institute should strengthen its clinical trials management activity to insure that researchers using investigational drugs comply with the approved protocols, drug distribution policies, and adverse drug reaction reporting procedures. A significant recommendation of the task force is that all affiliated investigators, including satellite investigators, be formally registered with the National Cancer Institute and in turn, with the Food and Drug Administration. These investigators need to be provided with a complete set of instructions or guidelines on their responsibilities in connection with these developmental drugs.

Of particular concern to this subcommittee has been the problem of the timely reporting of adverse drug reactions by individual investigators to the NCI and by the NCI to the Food and Drug Administration. The task force analysis of this difficult problem will be one of the topics we will discuss today.

The task force's conclusion that since 1975 there has been an overall response rate of approximately 9.5 percent in phase I experimental trials is disturbing. This low probability of response and the high risk of toxic effect of the drug are factors which might be made eminently clear to the patient through the informed consent process.

Late last year, I came to the conclusion that the Food and Drug Administration's Bureau of Drugs was in serious need of management assistance. I am pleased that the task force has made a specific recommendation concerning a management study of the Bureau of Drugs and its managers in regard to such areas as organization, personnel and staffing. Finally, I concur wholeheartedly with the task force's conclusion that the National Cancer Institute should more actively impose sanctions against wrongdoers. These sanctions are essential to provide a reminder to all those involved that the Federal regulations and procedures of both agencies must be adhered to. We can no longer allow these agencies to turn their backs on those whose disregard for proper procedure is risking patient safety.

I look forward to hearing from Dr. Brandt and other members of the task force in discussing their various concerns and recommendations. I commend the task force for their initiative and hard work.

For the first time since we began this inquiry more than a year ago, I believe that we can look to the cancer patients throughout this country and say with conviction that these problems are being addressed. I am certain that my colleagues on this subcommittee, who cannot be here because of conflicting engagements today, join me in the hope and determination that this hearing will provide some constructive solutions to insure improvement in these programs that are so vital to us all.

I would like to welcome the two witnesses that we have before us today, Dr. Edward Brandt, the Assistant Secretary for Health and Human Services, and Dr. Lowell T. Harmison, the chairman of the task force responsible for this particular report. Dr. Harmison is the Science Adviser in the Office of the Assistant Secretary for Health in the U.S. Public Health Service.

We would first like to hear from you, Dr. Brandt, and I believe you have a statement you would like to read in the record.

STATEMENT OF EDWARD N. BRANDT, JR., M.D., ASSISTANT SECRETARY FOR HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY LOWELL T. HARMISON, Ph. D., CHAIRMAN TASK FORCE, SCIENCE ADVISER, OFFICE OF THE ASSISTANT SECRETARY OF HEALTH, U.S. PUBLIC HEALTH SERVICE

Dr. **Brandt**. Yes, ma'am. Thank you very much, Madam Chairman.

Let me say that we are pleased to see you out of the hospital and back to work. We hope that you are recovering rapidly and successfully.

Senator **Hawkins**. Thank you.

Dr. **Brandt**. Dr. Harmison and I are here today to present to you the findings and recommendations of the task force which I appointed in October of last year. The task force was charged with: (1) assessing NCI management systems for monitoring IND's (investigational new drug applications); (2) assessing FDA's review of NCI activities relative to these drugs; and (3) developing recommendations for improvement that may stem from the findings of the task force. More than 700 documents were reviewed and over 45 persons, both inside and out of the government were interviewed.

This report represents not only a very thorough effort, but also an independent and unbiased effort. I did not attempt to influence the deliberations of the task force, and neither did NCI or the FDA. In fact, neither the NCI nor the FDA have commented or acted as clearance for the report. The report came directly to me from the task force and I have sent it directly to you. I have reviewed this report personally and find that I am satisfied that the task force has addressed the issues contained in my charge. I stand behind the report.

Before I discuss the recommendations of the task force, I want to recognize the contributions made in improving the management of both the NCI and the FDA that have been made by Dr. DeVita and Dr. Hayes. Great strides have been made by these two agencies in improving communications and tightening up the monitoring of clinical investigations using anticancer drugs.

As I said in my testimony in November before this subcommittee, the relationship between NCI and FDA and their individual systems of monitoring and regulation has been evolving over a number of years. Until the mid-1970's the system operated with an administrative laxness in certain areas that both institutions came to recognize as inappropriate. Since then, management in both NCI and FDA addressed these problems, the outcome of which has been the establishment in recent years of some special procedures between FDA and NCI with respect to cancer drugs. I also stated at that time that we fully recognize that problems have arisen and some still do exist. We are working to correct those as we have done in the past and we will continue to seek ways to improve the system. That was the charge of the task force—a charge that I believe they have fulfilled. I feel it is important to pause before the discussion ahead to recognize that we have all asked the NCI and the FDA to manage a difficult task in pursuing this Nation's cancer problem, and that they have, by and large, done so very well. The level of commitment by the agencies and their staffs deserves note.

Let me just insert at this point, Madam Chairman, that today we have announced that FDA has approved the first drug pump for implementation inside the body providing continuous drug therapy to an affected side. This pump can be used for a variety of drugs, but it is particularly used, and was used to deliver an antidrug to a person with liver cancer, thereby limiting the systemic toxic effect of that drug, and we are pleased that this development has occurred, as another step forward in our fight against cancer.

Madam Chairman, cancer is a most difficult subject—a subject charged with emotion; for all of us are touched by the devastating effects of cancer, a complex array of diseases for which we all hope science and medicine will control and cure. The task force has objectively reviewed a key component of our efforts to control and cure cancer. They found no systematic mismanagement. Both the NCI and the FDA have made significant progress in recent years and the recommendation of the task force will strengthen and improve that progress.

I will not attempt to discuss all of the recommendations given to me by the task force. The areas which are covered by the recommendations are:

The toxicology protocol;
Clinical trials;
Investigational new drug distribution and investigators;
Protection of human subjects;
Comparison of FDA-NCI relationships with FDA-industry relationships;
Communications problems;
Sanctions.

When I reviewed these recommendations, it was clear that they varied in content and in ease of implementation. Thus, I am categorizing the recommendations according to my view of their level of implementation difficulty. Those three categories are: Simple procedural changes. Complex procedural changes. Communications problems.

As an example of the first category, simple procedural changes are involved in emphasizing to NCI management their obligation to report violations of Federal rules and regulations to appropriate law enforcement authorities, for example, the HHS Inspector General.

As an example of the second category, relatively more complex procedural changes would be involved in the implementation of sanctions against the institution as well as the individual wrongdoer when multiple violations occur at a single institution—a change that may, and in my opinion does, require regulatory amendment.

As an example of the third category, the recommended study of the FDA Bureau of Drugs Divisions and Managers dealing with cytotoxic drugs and to examine areas about which questions have been raised, such as organization, personnel and staffing, budget, decisionmaking procedures, internal communications, morale, workload, filing system and paper flow, would be time consuming and require more effort.

I want to assure you that recommendations will be implemented as soon as possible and with this in mind I have established a preliminary timetable. Today, I am providing the NCI and the FDA copies of the task force report and a directive that within 30 days they provide me with a report concerning the implementation of the various recommendations including a timetable and a discussion of the implications for the implementation of the recommendations. Those recommendations without cost, personnel, or time constraints will be implemented immediately following my receipt of these reports.

Within 2 months from today, I intend to have a timetable for implementation of the bulk of the recommendations with a completion date of not more than 6 months from today. Certainly, Madam Chairman, we may find difficulties in maintaining this timetable, for example, if regulatory reform is required. But I assure you that this report and its recommendations are of a highest priority to me and I shall do my utmost to facilitate their implementation.

In closing, I would like to commend Dr. Harmison and the members of the task force for the tremendous effort they put into this project. They were dealing with an extremely complex and highly emotional issue. Yet they delivered to me a complete, factual, and objective report with implementable recommendations. They deserve our praise for what I know is a step to improving our efforts to combat this most dreaded array of diseases known as cancer.

Thank you. That concludes my statement, Madam Chairman. I will be pleased to answer questions.

[The prepared statement of Dr. Brandt follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES
Office of the Secretary
Washington, D.C. 20201

FOR RELEASE ONLY UPON DELIVERY

STATEMENT BY

EDWARD N. BRANDT, JR., M.D.

ASSISTANT SECRETARY FOR HEALTH

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON INVESTIGATIONS AND GENERAL OVERSIGHT

COMMITTEE ON LABOR AND HUMAN RESOURCES

U.S. SENATE

March 5, 1982

Madame Chairman and Members of the Subcommittee,

I am Dr. Edward N. Brandt, Jr., Assistant Secretary for Health, Department of Health and Human Services. With me today is Dr. Lowell Harmison, Chairman of the Task Force Review of Anticancer Investigational New Drugs. We are here today to present to you the findings and recommendations of the Task Force which I appointed in October of last year. The Task Force was charged with: (1) assessing NCI management systems for monitoring INDs (investigational new drug applications); (2) assessing FDA's review of NCI activities relative to these drugs; and (3) developing recommendations for improvement that may stem from the findings of the Task Force. More than 700 documents were reviewed and over 45 persons, both inside and out of the government were interviewed.

This report represents not only a very thorough effort, but also an independent and unbiased effort. I did not attempt to influence the deliberations of the Task Force, and neither did NCI or the FDA. In fact, neither the NCI nor the FDA have commented or acted as clearance for the report. The report came directly to me from the Task Force and I have sent it directly to you. I have reviewed this report personally and find that I am satisfied that the Task Force has addressed the issues contained in my charge. I stand behind the report.

Before I discuss the recommendations of the Task Force, I want to recognize the contributions made in improving the management of both the NCI and the FDA that have been made by Dr. DeVita and Dr. Hayes. Great strides have been made by these two agencies in improving communications and tightening up the monitoring of clinical investigations using anticancer drugs. As I said in my testimony in November before this Subcommittee, the relationship between NCI and FDA and their individual systems of monitoring and regulation has been evolving over a number of years. Until the mid-1970's the system operated with an administrative laxness in certain areas that both institutions came to recognize as inappropriate. Since then, management in both NCI and FDA addressed these problems, the outcome of which has been the establishment in recent years of some special procedures between FDA and NCI with respect to cancer drugs. I also stated at that time that we fully recognize that problems have arisen and some still do exist. We are working to correct those as we have done in the past and we will continue to seek ways to improve the system. That was the charge of the Task Force — a charge that I believe they have fulfilled. I feel it is important to pause before the discussion ahead to recognize that we have all asked the NCI and the FDA to manage a difficult task in pursuing this nation's cancer problem, and that they have, by and large, done so very well. The level of commitment by the agencies and their staffs deserves note.

Madame Chairman, cancer is a most difficult subject — a subject charged with emotion; for all of us are touched by the devastating effects of cancer, a complex array of diseases for which we all hope science and medicine will control and cure. The Task Force has objectively reviewed a key component of our efforts to control and cure cancer. They found no systematic mismanagement. Both the NCI and the FDA have made significant progress in recent years and the recommendations of the Task Force will strenghten and improve that progress.

I will not attempt to discuss all of the recommendations given to me by the Task Force. The areas which are covered by the recommendations are:

- The toxicology protocol;
- Clinical trials;
- Investigational new drug distribution and investigators;
- Protection of human subjects;
- Comparison of FDA-NCI relationships with FDA-industry relationships;
- Communciations problems;
- Sanctions.

When I reviewed these recommendations, it was clear that they varied in content and in ease of implementation. Thus, I am categorizing the recommendations according to my view of their level of implementation difficulty. Those three categories are:

- Simple procedural changes
- Complex procedural changes
- Communications problems

As an example of the first category, simple procedural changes are involved in emphasizing to NCI management their obligation to report violations of federal rules and regulations to appropriate law enforcement authorities, e.g., the HHS Inspector General.

As an example of the second category, relatively more complex procedural changes would be involved in the implementation of sanctions against the institution as well as the individual wrongdoer when multiple violations occur at a single institution — a change that may require regulatory amendment.

As an example of the third category, the recommended study of the FDA Bureau of Drugs divisions and managers dealing with cytotoxic drugs to examine areas about which questions have been raised, such as organization, personnel and staffing, budget, decision-making procedures, internal communications, morale, workload, filing system, and paperflow, would be time consuming and require more effort.

I want to assure you that recommendations will be implemented as soon as possible and with this end in mind I have established a preliminary timetable. Today, I am providing the NCI and the FDA copies of the Task Force report and a directive that within 30 days they provide me with a report concerning the implementation of the various recommendations including a timetable and a discussion of the implications for the implementation of the recommendations. Those recommendations without cost, personnel or time constraints will be implemented immediately following my receipt of these reports.

Within two months from today, I intend to have a timetable for implementation of the bulk of the recommendations with a completion date of not more than six months from today. Certainly, Madame Chairman, we may find difficulties in keeping this timetable, for example, if regulatory reform is required. But I assure you that this Report and its recommendations are of a highest priority to me and I shall do my utmost to facilitate their implementation.

In closing, I would like to commend Dr. Harmison and the members of the Task Force for the tremendous effort they put into this project. They were dealing with an extremely complex and highly emotional issue. Yet they delivered to me a complete, factual and objective report with implementable recommendations. They deserve our praise for what I know is a step to improving our efforts to combat this most dreaded array of diseases known as cancer.

Thank you. We will be happy to respond to any questions you may have.

Senator HAWKINS. I would like to find out more about the task force report, with several questions regarding the different procedures that were outlined in your report. Whichever one of you feels more comfortable addressing the questions, please go ahead.

On page 7 of the task force report, you mention the future NCI Drug Distribution and Cancer Treatment Plan. Do you have that page?

You indicate that plans to eliminate distribution of group C drugs to individual physicians will occur in 1986.

Why is 1986 the target date?

Dr. BRANDT. All right. The community cancer oncology program is a program that has been defined to put so-called CCOP's, or community clinical oncology programs all over the United States, blanketing the United States. We estimate that there will be, ultimately, about 200 such programs in place and in operation.

When they are in place, the class C drugs will be handled through the staffs of those CCOP's. We will begin in 1983, designating the first group. We anticipate that there is something less than 50 places where such a program could be implemented in 1983. We anticipate that the entire program will be implemented by 1986.

So that is really the target date when we can accomplish the full goal of control of the distribution of class C drugs. But we do anticipate getting in this operation in 1983.

Senator HAWKINS. How long will this take?

Dr. BRANDT. It will take us about 3 years. It will take about 3 or 4 years to get places up to where they are capable of carrying out this program.

Senator HAWKINS. What will be the effect of the elimination of distribution of these group C drugs to individual physicians?

Dr. BRANDT. We do not think there will be any effect, because in fact the cancer clinical oncology program will involve the individual physicians who are caring for patients in that region, and that will be the distribution point, so that in fact although we will eliminate the NCI sending the drugs to the individual investigators, in fact those drugs will be available to the people.

Senator HAWKINS. From the drug distributor?

Dr. BRANDT. No, from the people associated with the clinical oncology program in the communities. So that by blanketing the entire country, we should have—so that everybody will have access to the drugs, and to appropriate care.

Senator HAWKINS. Referring to page 11, would it be the recommendation of the task force that the Drug Master File have an overall index?

Dr. BRANDT. The Master Drug File is a very complex and somewhat large document that is divided into several volumes. There is, in fact, an index for each volume. An overall index could be accomplished solely by stapling, or pasting all those individual indices together, but I think that that is something that we certainly will look into, and see if it could be accomplished.

However, I again emphasize that every volume of the Master Drug File now does have an index.

Senator HAWKINS. Your report indicates that the memorandum of understanding between the NCI and the FDA is an appropriate document, and that there are problems related to its implementation.

What kinds of problems are you referring to?

Dr. **Brandt**. One, the basic difficulties I guess that one encounters in trying to put together, or trying to get two large complex entities, such as NCI and FDA, has to do with communications up and down the chain.

I think the memorandum of understanding, the basic problem that we have found was that—was the fact getting everybody who is involved in the anticancer drug problem, completely informed about the memorandum of understanding.

Dr. Harmison may have something to add to that.

Dr. **Harmison**. Madam Chairman, I would say that, the principal concern is one of communications. The need is for full awareness of what the memorandum of understanding contains at all levels within both NCI and FDA. Particularly, I think there is a wealth of scientific information that occurs in phase I meetings. This information is provided to FDA, but it is not provided by IND number. Therefore, it is not in that specific document. NCI and FDA are correcting this problem.

Senator **Hawkins**. This makes significant improvements?

Dr. **Harmison**. I think so. I think the areas that Dr. Brandt indicated, in the areas of communication, will significantly enhance the implementation of the memorandum of understanding by increased awareness at all levels within FDA and within NCI.

Senator **Hawkins**. One of the items that continually resurfaces during this entire report, is the toxicology protocol, which outlines the procedures for animal testing.

You indicate, on page 37, that strong objections to that protocol still remain among some FDA staff.

What are those strong objections?

Dr. **Harmison**. Principally, I would say that those objections have come over differences of scientific interpretation concerning the issues of histopathology and its submission to NCI. But I think, the task force felt, that in the course of the deliberate and open review process of the toxicology protocol that the folks who had concerns about the protocol had been adequately heard. Although, they did not agree with the preponderance of the scientific evaluation, they would proceed in utilizing and following the protocol. I think there would be a continued diligence on their part to identify and reidentify the importance of such things as the submission of the histopathology data, and other such scientific information to FDA.

In general, I think that they all agreed that the process was sound by which the protocol was developed. I think the task force found that the Commissioner plans to publish in the Federal Register, as we noted in our task force report, should provide useful comments.

So we were very pleased with what we found overall on the toxicology protocol issue.

Senator **Hawkins**. The recommendations that you made regarding the toxicology protocol are very pertinent. I agree wholeheartedly with your conclusion that there is a need to write down all that has been agreed to, and then to seek a grand round of approval in regard to the toxicology program. That recommendation was on page 12 in your report.

Would your recommendations also include publishing that particular document in the Federal Register?

Dr. **Harmison**. Yes.

Dr. **Brandt**. It is the intent of the Commissioner to publish the documents for comment.

However, I do think that it is important that we bear in mind that it is very unlikely that we are going to get unanimous agreement among scientists as to what is the appropriate protocol. So even so I certainly support its publication in the Federal Register, I certainly support seeking the widest possible input into its development refinement.

I have been around scientists to know that they do not always agree on everything. Maybe on anything. But——

Senator **Hawkins**. When do you think that the final round of approval might be sounded on the toxicology protocol?

Dr. **Harmison**. Specifically, we did not set a date for that. The process is now underway, as they review different facets of the protocol. We identified in our report that a mutual schedule should be developed between NCI and FDA.

We felt that rather than our articulation of a schedule that they should look at what is needed in the preparation for each of those separate reevaluations that they are going to do, and come up with their own schedule.

Senator **Hawkins**. Are you recommending that the toxicology protocol be periodically evaluated?

Dr. **Harmison**. Yes; I think that in this area, where new science and new information is occurring, it is extremely important that periodic evaluation be done. For example, it is important that the starting dose in the human that the toxicological protocol is predicting be regularly evaluated.

So we think that continuing review of the data, as I generated under the new protocol, will be very helpful. We found, in fact, a positive attitude on both FDA and NCI to accomplish the reassessment.

Senator **Hawkins**. In the task force analysis of the clinical trials involving these experimental drugs, you mention a serious problem, that we had discovered earlier, regarding notification of investigators in the field.

Did the task force conclude whether or not the National Cancer Institute even knows, as of this date, the names and locations of all its investigators?

Dr. **Harmison**. Yes; there is no question. I think that they do know their clinical investigators. As a task force, we approach this issue. There were variances as to exactly who was termed a clinical investigator. NCI knows all that are reported on the 1571 forms. It is the investigators in the satellite institutions, working under a registered principal investigator, that NCI might not have in their files.

Senator **Hawkins**. That was my next question.

Dr. **Harmison**. But they do have.

Senator **Hawkins**. Does the NCI have the names of the satellite investigators today?

Dr. **Harmison**. If they go to the principal investigator, this is known at the NCI, they can tell them who the investigators are.

We asked further, that these people (investigators) be listed as they rotate within those institutions, on the principal investigators' reports.

Senator **Hawkins**. How can the National Cancer Institute be expected to effectively monitor its investigators, when many of them report indirectly through cooperative groups and other contract investigators.

Dr. **Brandt**. I think that the issue there is that in the cooperative groups, particularly which are the sort of satellites, that in fact those people have a process and procedure for selecting people that work with them in the programs, and although those people are reported periodically to the NCI, at any one moment in time, the NCI may not have the names of everybody who is working in that. That is a situation that is easily correctable, simply by having them file a 1573.

However, since they rotate through, it is going to generate a lot of paper, and in fact, we will still really be dependent upon those experts in the cooperative groups to select, and they monitor and oversee all of those people, and it is not a large number of people, it is a relatively small number of situations that we are discussing.

But we are talking to Dr. DeVita about the possibility of having them go ahead and file the 1573, as they come into it, although it is probably really not necessary to accomplish the kinds of communication problems, because they are working directly under one of our registered investigators, with whom we do have contacts.

Senator **Hawkins**. In your report you indicate there are 5,000 clinical investigators——

Dr. **Brandt**. Yes.

Senator **Hawkins**. And that there are approximately 37,000 new cancer patients on experimental drug trials. I think it is a well taken recommendation that all of these investigators, including your satellite investigators, should be registered formally.

Can you possibly envision the NCI being able to adequately communicate with their investigators, if they constantly have to go through, as you said, the principle investigator who then in turn, contacts the satellite investigators? Can we be assured that the principle investigator shares the information?

Dr. **Brandt**. I think that in any—I think the answer to that is yes, having been associated out in the field, with cooperative groups, that these groups meet very regularly to talk about the problems, just as they have phase I and phase II meetings now with the principal investigators who are involved. So that I think in any event, that there is no question that all those people are getting the information that is coming from the NCI right now.

Now, I certainly understand that it might be helpful for form 1573's to be filed, and as I say, Dr. DeVita is certainly looking into that at the moment.

Senator **Hawkins**. In the past they were not. Are you telling me that they are now?

Dr. **Brandt**. In the past they were not, and they are not now. In the satellite programs we do not require all of them to file a form 1573, as long as the supervising register is up to date.

Senator **Hawkins**. But you are discussing with Dr. DeVita your suggestions that it would be a good idea for all of them to fill out a 1573?

Dr. **Brandt**. Yes, madam, we are.

Senator **Hawkins**. Good. The task force itself was critical of the increase in the number of patients currently involved in some clinical trials that have consistently shown no real promise, this is on page 15.

At the present time how is a determination made as to the number of patients who will participate in a given study?

Dr. **Brandt**. The question of the number of people in a phase I and phase II study is dependent, in large part, upon the kind of symptoms.

For example, if one has drugs to treat carcinoma of the breast, and you are looking for response to that on, let us say, a phase I trial, ordinarily you would ideally, what you would like to have is 14 or 15 identical patients walk through the door so that you could test them and determine whether or not they are going to respond.

In fact, the patients that get on these trials will vary with respect to the extent of their illness, with respect to previous treatment, with respect to whether or not they have bone involvement, or do not have bone involvement, so that it is not possible to really predict in advance exactly how many patients you will need in order to determine whether or not there is going to be a response.

However, at the same time, it is clear that you do not want to keep patients on a drug where there is no apparent hope for a response from that drug. So it is, in large part, a continuing judgment process, although clearly those things need to be examined periodically, to make sure that the best judgment is being used, and we certainly are sympathetic with that.

Senator **Hawkins**. You recommended in your task force report that the NCI should conduct an analysis of the treatment results at appropriate intervals to define the effectiveness of the drug.

Dr. **Brandt**. Yes.

Senator **Hawkins**. How would you anticipate that this might be accomplished?

Dr. **Harmison**. I think, Madam Chairman, the importance that the task force attached to this area is articulated in about three recommendations addressing the patient accrual and monitoring of patient accrual. They were directed to insure that there was full awareness of what is occurring, and that NCI does receive reports regularly and consistently from their monitoring service about the numbers of patients.

We wanted to add emphasis and importance to this area to be sure that there was a repeated analysis as data are accumulated. In other words, the patient's response to the treatment was in fact being observed, as the number of patients increased in both phase I and phase II trials.

And second, that as the response rate was determined for specific types of tumors, and that as they moved through the tumor panels, in the different evaluations, that that assessment be made. This will raise the level of concern and the need to have those analyses as data accumulates.

We emphasized in a positive sense that NCI is very concerned and very aware of the need to do this. We wanted to add emphasis to what they are undertaking.

Senator **Hawkins**. In your report, under conclusions and recommendations regarding the NCI's clinical trials management system, you pointed out that a management group should be created to ensure that the investigational drugs under NCI sponsorship are handled properly with approved study protocols, drug distribution policies and the proper reporting of adverse drug reactions.

In our investigation in 1981 we found that NCI itself was not properly reporting adverse drug reactions to the FDA, and the Director indicated a lack of appreciation for the fact that this was in violation of present Federal regulations. My concern today is, if the management group is regulating the reporting of these procedures, who is going to regulate the NCI itself?

Dr. **Brandt**. Well, I think, Madam Chairman, that the regulation of the NCI with respect to the anticancer drugs is clearly, in the first place, the responsibility of the Director of the NIH, and myself, but in addition it is the FDA. They are the ones who are responsible for investigational new drugs throughout the country, and their monitoring.

I think the issue with the clinical trials management system has been one of attempting to work with investigators, to point out to them that the criteria required for adverse drug reactions are perhaps different than most oncologists would suspect. These drugs, when they are used in humans, are known to cause side effects. They are, in fact, cytotoxic agents. That is what we have available.

Every modality that we have for the treatment of cancer, including radiation and surgery, as well as the drugs, have side effects, and have some toxicists associated with them. In most drugs that is not the case.

If you are testing an antihistamine, one does not go to human trials if you have no side effects, and therefore when a side effect shows up it gets reported rather quickly.

The issue that has to do with attempting to report more and more these side effects to the FDA, recognizing that in some instances they will turn out not to be side effects of the drug, but part of the patient's illness.

In any event, that issue, I think, is one that we are currently working on, and in my opinion we will handle soon.

Dr. **Harmison**. Madam Chairman, if I might address this specific point.

We felt that the vital nature of the work carried out by the investigational new drug branch and the clinical branch, should be annually looked at by an outside scientific advisory committee. This would provide, I believe, the additional interest that you were concerned about. It would include review of the management activity that would look at the responses of the clinical trials management system. The outside scientific advisory group would prepare an annual report.

Senator **Hawkins**. Your report shows that NCI has acted improperly in the past.

Let me state first that clinical investigators discovering an adverse drug reaction, have failed to report to NCI, and instead some investigators are working out possible ADR's for medical journals—and on and on.

The last line on page 65 of the report states: "These failures pointed to critical misunderstandings on the part of investigators and NCI about requirements of ADR reporting with investigational new drugs."

Can we be sure that they now have the message and that you are taking active oversight?

Dr. **Brandt**. I think if you turn to page 66, it says NCI recently revised its procedures for adverse drug reaction reporting and evaluation, as depicted in the figure there, and in October a letter was sent by Dr. DeVita to all clinical investigators, again reminding them.

Again, I think it is—the issue was, I think, not a—in any sense, deliberate, or in any sense malicious, but was in fact a failure of a misunderstanding because of the perceived differences in the definition of an adverse drug reaction between these agents and most other drugs.

Senator **Hawkins**. Is that——

Dr. **Brandt**. But it is something.

Senator **Hawkins**. Did that letter go to the satellite investigators?

Dr. **Brandt**. I am sorry?

Senator **Hawkins**. Was that information distributed to the satellite investigators also?

Dr. **Brandt**. Yes.

Dr. **Harmison**. To all investigators.

Dr. **Brandt**. And we will in fact stay on top of this, I can assure you, and work closely with the FDA, to be sure that the adverse drug reactions are known, and are reported.

I think at the same time we have to recognize that many of the communications that are turned in, turn out not to be adverse drug reactions, that is, turn out not to be the drugs that is the cause of, but in fact the disease process that is underway. These are terrible illnesses, and they cause an awful lot of problems.

But there is no question that the reporting will in fact pick up considerably.

Senator **Hawkins**. I was heartened by your recommendation that the Bureau of Drugs should include all of the NCI investigators for review on a routine basis.

Does the task force share my concern that all of the NCI sponsored drug investigators, including those with cytotoxic drugs be reviewed on a routine basis?

Dr. **Brandt**. Yes, we agree with that, and they will be.

Senator **Hawkins**. You make a recommendation that the NCI should develop a set of instructions or guidelines for the investigators.

Do you envision a situation where every investigator, including those satellite investigators I am concerned with, would get a copy of these instructions?

Dr. **Harmison**. Absolutely, Madam Chairman.

Senator **Hawkins**. That is the kind of answer I like, absolutely. I love that kind of answer.

What about those investigators who do not file an updated form 1573, are you going to lose some of these guys?

Dr. **Brandt**. No investigator will be permitted to conduct clinical trials without an up to date and acceptable 1573.

Now, we do have to recognize that on occasion there will be an instance where there will be a physician who is competent to use the drug, who may need it for a specific patient, whose 1573 may not be up to date. We will update that over the telephone, and try to get the drug to them, so that we can get that patient taken care of.

This is an exception that is permitted in the regulations for FDA, for specific instances, where a patient may benefit dramatically from a drug, and where the only problem is getting a form signed. We can get that information over the telephone, and permit it to go ahead.

Senator **Hawkins**. As a layman, it just seems so simple—comparable to the use of a credit card, after a credit check is run and we are told that we cannot use the card.

It just seems that it could be almost instantaneous, if it is programed properly, that when investigators call in on the telephone asking for something, you would know at once, by pushing a button.

Dr. **Brandt**. Yes, we do now, and that information is there.

I think the question has been the issue of the compassion, that of IND, as it is called, that is the issue. Plus the satellite investigators that you have talked about.

But the major issue is when there is a good reason to permit, we have a number of competent oncologists around the country who are competent to use these drugs, and who do use them, but who may use them on an irregular basis, and some of them do not keep their forms completely up to date, because they do not anticipate using them.

At the present time, we will permit, as an exception, under a compassionate IND, one of these people to use it, as long as we update their 1573's over the phone, and make sure that they are still in there. That procedure is currently operational, and we are going to encourage all of those people to keep their 1573's up to date, even if they do not anticipate using them.

Senator **Hawkins**. Surely. On page 21, you characterize the drug distribution system as having a serious defect.

Was it the task force's conclusion that there is significant secondary distribution, that is, drug distribution beyond approved protocols?

Dr. **Brandt**. The question is an understanding of a series. There has been leakage, there has been no question about that.

Senator **Hawkins**. There has been what?

Dr. **Brandt**. There has been leakage. There have been drugs that have been sent out for protocol and then used in patients who do not get that protocol. That procedure has already been tightened up considerably.

At the present time, what we are doing is to estimate the approximate quantity of drugs that will be required to conduct a clinical trial in sending out approximately one-half of that at the beginning of the study and then monitoring it. We do require them now to send back any drug that is not used, and since we do note the amounts that they have, why we can again get a rough check to be sure that they are complying with that. I think we will cut the leakage down remarkably by that action.

Dr. **Harmison**. I would agree.

I think there is one point, Madam Chairman, the point that there was no way we could identify documenting the unreturned drug. In other words, when an IND is stopped. They return the unused drugs to NCI. The question is being able to compare how much was actually used and who used it against the amount shipped and returned. This is why we felt that a high priority should be given to implementing the current system. I should point out that NCI has moved a great distance to implementing the drug distribution system and control system. The task force found that they were proceeding rapidly in carrying out that effort.

We simply added our emphasis to the priority of getting that drug control system in place so that they could have instantaneous knowledge of who had received drugs.

Senator **Hawkins**. The question of how much had been used was the problem?

Dr. **Harmison**. Yes. NCI knew how much had been shipped and to whom, but not how much used and by whom.

We wanted to tie both together, that is how much had been used and how much had not been used, and by whom. The task force felt the need for the requirement for records by the investigator so that on a site visits they could be checked and the information verified.

Senator **Hawkins**. On page 22, you state that "Investigational drugs that are not intended for human use have, on rare occasions, wrongly been given to patients," and that tighter control on the distributions of drugs alone will not solve this problem. You mention education and labeling as being a possible solution.

Is there any current effort underway to encourage this education or to label the materials properly?

Dr. **Brandt**. Yes to both questions. They are labeled and we are instructing all of the investigators that are using drugs that have not yet been approved for human use, not to use them in humans, even though their own data—now, of course, the most famous case of that was the one in Houston. I think in that example it has been dealt with and I believe that the message is getting across pretty clear with the kind of attention that that particular case got, attracted a lot of attention, as well as our own efforts at trying to educate.

Dr. **Harmison**. I think, Madam Chairman, the point we wanted to emphasize in the report was that if an investigator intended to violate a regulation, there is not much way that you can design a system to address this type of violation.

Senator **Hawkins**. But you can catch him?

Dr. **Harmison**. Yes.

Senator **Hawkins**. If someone intends to commit a crime there is not much that you can do to prevent it, but you can now find him?

Dr. **Brandt**. Yes.

Senator **Hawkins**. I would like to ask some specific questions on the drugs Methyl-CCNU and 5 Methyl-THHF.

In your task force report, on page 8, it is indicated that the National Cancer Institute did distribute a brochure to physician-investigators recounting the results of the animal studies.

Now, I am wondering if the brochure that was distributed to investigators included all of the results of the preclinical animal tests involving Methyl-CCNU?

Dr. BRANDT. Well, the policy with respect to the brochures that are sent to the investigators with respect to the drug includes summaries of the free clinical information so that they can look it up. The IND that is filed with the FDA, of course, includes all of the information and that—those IND's are available to any investigator who chooses to read them.

Methyl-CCNU problem is partly a timing problem because the renal effects of Methyl-CCNU were seen in animals and was included in the original brochure that went out to investigators. However, when the drug went into human trial and no cases were found, then the brochure was altered to indicate that no renal toxicity had been noted. It was only after the case showed up that again the issue was changed again.

So I think the Methyl-CCNU issue is partly when you took a look at it as to what information was available to the investigators.

Senator HAWKINS. Would you agree that it is absolutely essential that all physician investigators in the field have a complete and thorough information source regarding side effects that have been observed in either clinical or preclinical testing?

Dr. BRANDT. I think the investigators need all the information that we can make available to them.

I think that we have—the question is only really are we going to summarize it and present it to them, or are we going to make the total IND and the total case reports available to them? But there is no question in my mind that all of our investigators need to, when they begin a study, need to have all the information that is there and they need to be periodically informed of both positive and negative findings resulting from studies by other investigators. And we will, in fact, make sure that that occurs.

Senator HAWKINS. Your report indicates that NCI decided to study the Methyl-CCNU reaction reports further before contacting the FDA. This hesitation was done to ensure that the renal insufficiency was indeed related to Methyl-CCNU.

Should not the NCI have advised the FDA, as soon as it became aware of any findings associated with the use of the drug that may suggest side effects? If we err, should it not be on the side of caution?

Dr. BRANDT. Yes. I think there is no question. When we hear from an investigator of a potential side effect from the drug, that the FDA should be notified that we are now doing that. And but again——

Senator HAWKINS. What are the sanctions that are imposed if investigators fail to report it?

Dr. BRANDT. Their 1573 will be pulled and they will not be permitted to participate.

Senator HAWKINS. Further?

Dr. BRANDT. In further studies, that is correct.

Senator **Hawkins**. Were any sanctions imposed on the case we discussed?

Dr. **Brandt**. In the Methyl-CCNU case, no, ma'am.

Senator **Hawkins**. Why?

Dr. **Brandt**. It is hard to go back and reconstruct that. I think it was an issue that, at the time of all of this, it was not clear to the people involved that this was an adverse reaction from the drug. It was thought, in fact, to be a part of that patient's illness and not an adverse drug reaction.

I think that issue will hopefully not ever arise again.

Senator **Hawkins**. With regard to the drug 5 Methyl-THHF, which was a substance administered to the six patients at M. D. Anderson Clinic at a time when it had only been approved for use in animal studies, did the task force reach a conclusion as to why it took more than a year before the improper use of this drug became known to the NCI? It is on page 9 of your report.

Dr. **Brandt**. Yes. It depends how you measure it.

It was over a year from the time that the drug was used in humans at the M. D. Anderson until something was done. However, the NCI did not become aware of the fact that 5 Methyl-THHF had been used in humans until approximately June. They immediately went into action and within 6 months sanctions had been imposed against the two investigators involved, actually the investigator who was studying it in animals and the commission who used it in people, both of them had sanctions imposed by the NCI as soon as they verified that it had occurred.

Senator **Hawkins**. The drug was shipped to the investigators with clear warning not to use the drug in humans——

Dr. **Brandt**. That is correct.

Senator **Hawkins**. And that this study was in clear violation of both FDA regulations and the NCI contractual agreement?

Dr. **Brandt**. That is right.

Senator **Hawkins**. So it does demonstrate deficiencies in the drug program?

Dr. **Brandt**. Well, again, I think that example is one that clearly was a hole in our net. Again if an investigator wants to do something wrong, I do not know of any way that we can completely keep them from doing that. I think we can work very hard to try to minimize the opportunity for that occurring. We certainly can take sanctions against the people who are involved in that kind of wrongdoing and we will.

I would like to be able to tell you that there will be absolutely no violations by any investigator in the future, and I certainly hope that is true. And I think we will work to try to keep it that way, humans being what they are, I am sure somebody will want to do something that we may not be able to prevent. But I believe we are getting the word out to all of the people involved in this that we will not tolerate any kind of violations of our rules or institutional rules as far as that is concerned.

Senator **Hawkins**. I understand that one of the things you recommended was to recover the Federal funds which were used to pay for the improper study.

Has there been any action taken to recover the money?

Dr. **Brandt**. Yes. We have recovered the full amount of money from M. D. Anderson. It has been paid.

Senator **Hawkins**. We discovered similar problems involving two other substances, DHAD and DCF, as you recall from the other hearing.

Were there other serious problems involving specific drugs which are not mentioned in your task force report?

Dr. **Harmison**. No, Madam Chairman. We did not go into each of those cases. We were concerned primarily with the identification of general problems and focused on the management issue and on the regulations issued from FDA. We thought that the OPRR, NCI, and FDA would be pursuing those cases.

Senator **Hawkins**. The chart in figure 4 in your report describing the adverse drug reaction reporting system looks good on paper. I am just concerned how it might work in practice.

The chart follows page 26 in the book. Does this drug reaction reporting system indicate to you that NCI will notify FDA immediately?

Dr. **Harmison**. Yes, Madam Chairman. When they receive a reaction that is termed alarming by the investigator, they immediately call it to FDA. I have discussed this issue, after receiving the chart, with the people engaged in ADR monitoring and I am satisfied that it is working as outlined in this chart at the present time.

Senator **Hawkins**. And then immediately thereafter, all relevant investigators will be notified?

Dr. **Harmison**. Yes.

Senator **Hawkins**. The most important question facing the task force and this subcommittee, of course, is the protection of patient safety. I share your belief that the concern is whether the low probability of response and the high risk of toxic side effects of the drug are made clear to the patient through the informed consent process. We had a lot of testimony in our hearings about that, and I have discussed it at great length in the last 2 months with a lot of patients.

It is essential that if the word "informed" is to have any meaning in this situation, then the low probability of response and the risk of toxic side effects must be made known to patients. I think we all agree to that.

Do you agree that the patient should be told that there is an overall response rate, that is, a successful response in the patient of only 9.5 percent in phase 1 experimental trials?

Dr. **Brandt**. I think, without question, the patient should be told not only the low probability of success but also the side effects, and so forth, assuming the patient wants to know that.

Senator **Hawkins**. What do I know if you tell me it has a 9.5 percent success rate?

Dr. **Brandt**. I think it has to be explained to them that that means that roughly 10 patients out of 100 will experience favorable response from the drug.

Now, clearly, that changes as you move through the study. That is if you—if the first patient shows a favorable response, you can tell the second patient that there is a 100-percent rate as you move on through. Informed consent is both a process and an act. By that I mean that as you gain information, once a patient agrees to participate in a study, and I firmly agree that they should be given every bit of information that they want to have before they make that agreement, that you still have the obligation to continue to inform that patient as they go along so that if, indeed, they feel like withdrawing at any time or they feel like changing at any time, that can be done.

We believe that the clinical investigators should form a patient-physician relationship with the patients that are in these studies and that they should treat them as they would their patients. And we believe that, in general, and indeed in virtually every instance, that is in fact the case. But I really do think it is important to emphasize, I said a couple of times, that they should know as much as they know.

Personally when I go to the physician, I do not want him to tell me anything. I just want him to take care of me because it scares me.

Senator **Hawkins**. You have a little sign hung on you stating "feed me"?

Dr. **Brandt**. Yes. Correct. Show me where to sign.

Senator **Hawkins**. That is unfortunately the way most of us feel until we have had adverse reactions, and then you want to know why. It is our responsibility to protect patient safety. I do not know that the 9.5-percent rate explained in phase 1 experiments is understandable to the patient. We will have to rely a great deal on the physician in his one-on-one with the patient. I agree with the task force report where it states it is the physician's responsibility to modify this consent form to reflect the current information on adverse reactions to the drug.

I am all in favor of that and I also feel that the doctor should speak a language that the patient understands It can be done. I just want to know if all the physician investigators are aware of this responsibility? Is it going to be written in plain English?

Dr. **Brandt**. I think that every clinical investigator in this country, irrespective of whether they are dealing in this area or in other areas, certainly are aware of that responsibility. We have focused a great deal of attention on that. We are focusing more in general at the NIH to again emphasize and I might say to again emphasize to all clinical investigators that informed consent is their responsibility to obtain, and by that we do mean informed, and that they should be sure that people who are their partners in research, in fact, are actually informed when they agree to become——

Senator **Hawkins**. Do you believe that consent forms are now being updated with new information?

Dr. **Brandt**. We have—the information that we have, of course, is principally from conversations with the investigators, and that comes about in meetings. And I think the answer to that is that generally yes. I do not know of—now, periodically, a specific instance will pop up where people feel that they were not informed at the time. I certainly regret that, but I think most of the—indeed virtually all of the clinical investigators take that responsibility seriously and do their best to communicate with the patient about that.

Senator Hawkins. You have paid great attention to the problems and failures of the IRB's, the Institutional Review Boards. . . .

Dr. Brandt. Yes, madam.

Senator Hawkins. As protectors of human subjects. You indicated that part of this failure is directly related to the absence of specific direction and education of the members.

What steps can be taken, or what steps are you taking to ensure that the IRB's perform their appropriate tasks?

Dr. Brandt. Well, we have two mechanisms for this within the Public Health Service.

Senator Hawkins. Tell me how it is supposed to work first.

Dr. Brandt. No patient or no human is to be exposed to an experimental protocol or to participate in experimental protocol without review of that protocol and review of the process and forms to be used to obtain informed consent without the approval of an Institutional Review Board.

The Institutional Review Board is set up to include not only scientists but also laymen, including representatives of the law and of theology and, hopefully, of other aspects of society. The objective is to be sure that the risk that the subject will be exposed to by participating in this protocol is not going to endanger them in any way, and that when appropriate that they receive some potential benefits from it. Every investigator is expected to and, in fact, if they receive a grant from the Public Health Service, is required to have approval of the Institutional Review Board before they initiate their research. And if at any time they make any changes in that protocol, any proposed changes, that they do that. They may go before the IRB again.

Now, the Institutional Review Boards are monitored by the institutions and, in fact, they are required to be responsible to as high an administrative official as possible. Generally speaking, in most universities, that is the vice president. It can, in some cases, be the president of the institution. That is the way they are supposed to work.

Now, in addition to that, the IRB's are required to monitor the progress of the research. That is, they are to look to see how many people are participating in the protocol, that is as subjects; whether or not there have been any adverse reactions; what has been done if there have been any adverse reactions; and any modification in the protocol that might be indicated as a result.

Our observation of the IRB's has been that they perform quite well. Now, the circumstances dealing with the IRB's in this program has been one alleged instance of an investigator not submitting his protocol to the IRB or not at least adhering to the protocol that was approved by the IRB. And one example, the one that you cited earlier, at the M. D. Anderson Hospital where the investigator did not even go through the IRB before this study happened. Institutions are supposed to have in place mechanisms to prevent the latter from occurring, and the former, too, as far as that is concerned. And we have worked with M. D. Anderson to be sure that their procedures are tightened up and that that situation will not occur in FDA because they have so many more institutions involved. NIH does selective site visits and selective audits of IRB's to look for deficiencies and so forth in their operation. So we have two kinds of systems in general. We believe it is the institutional responsibility to monitor their people in the performance of any kind of experiments, including those using animals or people. And they do it well with clearly some few exemptions.

Senator **Hawkins**. On page 34 of the report, you stated that the task force could not assess comments that FDA accepts less chemical information, less evidence of agent purity and less and tardy paperwork submitted from NCI.

What were the difficulties you experienced in trying to assess the quality of paperwork submissions provided the FDA by the NCI?

Dr. **Harmison**. It was our feeling in reviewing that we needed to pull together an enormous amount of material regarding the detailed chemistries that had been presented and to assemble that and to have a full complement of chemists concerned with those areas in the leading edge of that science for its evaluation. After looking very carefully at that material, we concluded, as you will find in the recommendation, I believe it is on page 36—I am sorry—the recommendation is on page 34, we felt that a separate task effort bringing together those scientists who felt that there were differences directly to discuss that under the auspices of an organization other than NCI or Bureau of Drugs would be most appropriate.

Senator **Hawkins**. Take it away, is that what you are saying?

Dr. **Harmison**. No; I think because we found in a careful, look at the material that was presented from NCI that they felt that there was high quality in the chemistry and the purity of the information presented. We found information, at least conversations and discussions with the task force, that some FDA staff members felt differently than what we felt. We wanted to highlight this issue and have them focus on these issues as they get together to try to resolve the difference in perception.

We are not convinced that there is or is not a specific problem.

Senator **Hawkins**. In the recommendations of the task force, you indicate that the NCI meetings should be structured for free exchange of ideas on the science and medicine of cytotoxic drugs while insulating those discussions from FDA regulatory functions of attending FDA staff.

Does this mean that the task force believes that the FDA staff should not be present?

Dr. **Harmison**. No; absolutely to the contrary. We felt that it was important that they participate in the science and in the exchange of information so as to really get to the heart of the available scientific and other pertinent information, but not be put directly on the spot of saying this is or this is not acceptable from an FDA regulatory standpoint in the discussion of the science and the data base. We felt that they should not encumber their direct involvement to get full exposure, and if NCI or others had a question about the specific degree of applicability for a particular FDA requirement.

Senator **Hawkins**. Many of the facts uncovered in 1981 indicated that the Bureau of Drugs had significant problems in management and administration at the upper levels. I was pleased to see that you recommend that the Office of the Assistant Secretary of Health, Office of Management, should undertake a study of the

Bureau of Drugs and of its managers. And I would like to know when such a study might be accomplished.

Dr. **Brandt**. We would hope to—I have not discussed this with Commissioner Hayes at an appropriate time to begin it. I would hope we would begin it within the next 2 months. We are currently looking for a new Director of the Bureau of Drugs, and it would be hopeful to begin that study so that early in their tenure, his or her tenure as the Director, so some of these changes could be implemented. We hope to get it underway as soon as possible. I just have not talked to Dr. Hayes about the appropriate time to do it from his standpoint.

Senator **Hawkins**. You made a final conclusion in your task force report in regard to sanctions, and you point out that you have to punish the wrongdoer to remind the others of the requirements of these rules and regulations and to defer potential wrongdoers who are obviously tempted on a 24-hour basis. Those kinds of recommendations that were made in the past really had very little success.

What do you think the task force or this subcommittee can do to finally drive the message home that real sanctions need to be imposed when the rules are disregarded?

Dr. **Brandt**. The problem again extends beyond this particular aspect. I am distressed about some of the problems that were uncovered in the last couple of years concerning scientists and scientific activities.

We currently have underway within the NIH generally a look at the whole issue of what should we do about—clearly—the individual must be punished, and the other side of that is what happens to the institution as well? So we are, in fact, pulling that together generally for the NIH and ADAMHA and not addressing it specifically to this problem, but including obviously this type of research in that.

I think that the—that moves slowly in part because clearly we want to be sure that when you impose the kinds of sanctions that we impose, which basically means that you, for all intents and purposes, are ending a scientist's career, that you be fair and that you be right, and we are, in fact attempting to develop a process that will perm the people to be well served by scientists, at the same time not unfairly accuse or punish someone who is innocent of wrongdoing.

Senator **Hawkins**. That is the purpose of justice overall, whether it is in the scientific community or not.

Dr. **Brandt**. I think the standard is partly the issue.

At what point do you, in fact—what kind of standards of behavior are we going to require from the scientific community, and I think it is——

Senator **Hawkins**. It has been assumed that scientists have the highest standards.

Dr. **Brandt**. I think that is correct, and it is my own personal hope that we could get back to that soon. I think that, quite frankly, that most—I mean the vast majority of scientists are clearly people of high ethical standards and people of great talent and have served the American people very well.

One of the reasons that we are caught in the sanction business right now, in the dilemma, is that it is only recently that we have had to use it. It is only recently that these issues seem to have occurred or at least discovered, so we kind of got caught in a sense by having some wrongdoing that nobody ever anticipated would happen and, therefore, no process or procedures were set up to deal with it. We will have them in place soon.

Senator HAWKINS. Dr. Brandt, I was most impressed with the quality of the recommendations. I am concerned how we will ensure that they are implemented.

We have a lot of papers in my office, as do you, and a lot of work to do, and having now put these recommendations on paper, what do you believe is the weight and the status of these recommendations at HHS?

Dr. BRANDT. I am sorry?

Senator HAWKINS. What do you feel will be the weight and the status of your recommendations at the Department of Health and Human Services?

Dr. BRANDT. Well, my plan for the implementation is as follows: We will, within the Department, the Secretary has certainly given me the necessary authority to move and to do what is best to resolve any problem. But what I intend to do is to, within the next 60 days, develop a complete timetable for each of the recommendations and begin the implementation of those that can be done without cost or personnel or other kinds of procedures that are required within 30 days.

Senator HAWKINS. Is that a written report?

Dr. BRANDT. Yes; there will be a written report submitted to me by both the FDA and NCI concerning these regulations. I intend to keep you and your subcommittee members fully informed of the progress in the implementation report and will be making full reports to you.

Senator HAWKINS. Do you have a timetable?

Dr. BRANDT. Not yet, but I will have a timetable in your hands in 60 days.

Senator HAWKINS. Thank you.

If you encounter any significant obstacles in your implementations, will you inform us?

Dr. BRANDT. Absolutely.

Senator HAWKINS. Because even though we are not from the IRS, we are here to help.

Dr. BRANDT. Any time that I see that you can help me, I will certainly call you as well.

Senator HAWKINS. I appreciate your willingness to be here today, and I know that with the amount of work that you have to do in that huge agency that it takes an awful lot of time to have the meetings and write the reports that your task force brought to us today.

I am disturbed that I was told, as I entered the room, that a reporter had interviewed you and that your comments were that there was nothing significant here to——

Dr. BRANDT. I think that comment is somewhat out of context, Madam Chairman.

You came into the room while I was talking to him, and I quit in the middle of a sentence and walked off.

Senator **Hawkins**. I am giving you an opportunity to finish the sentence because I feel they are significant, and I thought you should have the opportunity to finish that sentence.

Dr. **Brandt**. I think there is no question that the recommendations, that there are significant recommendations in here, but I think in terms of the total implementation of them, they are not significant problems in getting most of these implemented and in place. That is what I was intending to say to him.

I am still new enough up here that I have not learned that you do not walk off in the middle of a conversation with a reporter. It can get you into a lot of trouble.

Senator **Hawkins**. I have the same problem. I think we all do. I would like to give everything out in writing. I have a friend who will not be asked any questions by the press or will not answer any of them orally. He will answer them in writing. Obviously he is not in politics. I do not want the recommendations quickly forgotten. I think you understand we have had many directives on how they should be implemented. It is a big bureaucratic group and dealing with scientists is difficult because they are individuals who have succeeded in their own avenues and have rarely had anyone to answer to and who have not been in a structured format.

Dr. **Brandt**. I have no illusions that those recommendations that depend upon getting communications and better communication processes and better understandings and attitudinal change are going to be easy to implement, nor are they going to be done quickly. But certainly the process will get underway.

Senator **Hawkins**. Well, we appreciate that first giant step and look forward to working with you, and appreciate your initiative and diligence. I want to let the public know as well as all those who are so vitally interested in this subject—it touches every family today, I think, in the United States—that we still recognize and support the need for investigational new drugs, but that we have taken steps to ensure that the patient's welfare and integrity and safety are protected at every step of the treatment.

Thank you so much.

Dr. **Brandt**. Thank you very much.

[Task force report submitted for the record follows:]

VOLUME I

SUMMARY REPORT

on

ANTICANCER DRUGS: NATIONAL CANCER INSTITUTE'S DEVELOPMENT AND THE FOOD AND DRUG ADMINISTRATION'S REGULATION

by

Task Force on NCI-FDA
Investigational New Drugs Task Force

January 8, 1982

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

SUMMARY REPORT
on the
ANTICANCER DRUGS:
THE NATIONAL CANCER INSTITUTE'S DEVELOPMENT AND THE FOOD AND DRUG ADMINISTRATION'S REGULATION

Report of the

Task Force on National Cancer Institute-
Food and Drug Administration Investigational New Drugs

January 8, 1982

Lowell T. Harmison, Ph.D., Chairman,
Science Advisor, Office of the
Assistant Secretary of Health,
U.S. Public Health Service

Lionel Bernstein, M.D., Ph.D.,
Vice-Chairman,
Former Director, Lister Hill
National Center for Biomedical
Communications, NLM, NIH

John Duffy, M.D.,
Deputy Associate Commissioner for Health Affairs
(Professional Relations), FDA

John R. Farrell, M.D., Operations
Management Staff, Office of
Management, OASH

David W. Fraser, M.D., Assistant
Director for Medical Science,
Bacterial Diseases Division,
Center for Infectious Diseases,
CDC

Paul J. Gilligan, M.H.S., Senior
Management Analyst, Office of
Management, OASH

Robert S. Gordon, Jr. M.D., M.H.S.
Special Assistant to the
Director, NIH

Jerome Levine, M.D., Chief,
Pharmacologic and Somatic
Treatments Research Branch,
Division of Extramural
Research Programs, NIMH,
ADAMHA

Joel M. Mangel, J.D., Deputy
Assistant General Counsel,
Public Health Division, Office
of the General Counsel, Office
of the Secretary, HHS

Lawrence R. Rose, M.D., Associate Director for Professional
Services, National Center for
Health Services Research, OHRST

Joan P. Porter, M.Sc.,
Executive Secretary,
Special Assistant to the
Director, Division of
Research Grants, NIH

Also working closely with the Task Force: Jack Blaine, M.D., Pharmacologic and Somatic Treatments Research Branch, Division of Extramural Research Programs, NIMH, ADAMHA; Richard J. Riseberg, J.D., Chief, National Institutes of Health Branch, Office of the General Counsel, Office of the Secretary, HHS; Anita Eichler, M.A., Office of State and Community Liaison, NIMH, ADAMHA, and Irene Shifren, Ph.D., formerly of ADAMHA.

Carol Peterson, Management Analyst, Office of Management Support, NIMH, ADAMHA; Judy Fouche, Editorial Assistant, Division of Personnel Management, NIH; Rebecca A. Dick, OASH; and Ellen Byrd, Division of Research Grants, NIH, also assisted the Task Force.

ABBREVIATIONS

A

ADAMHA - Alcohol, Drug Abuse and Mental Health Administration
ADR - Adverse Drug Reaction
ADRC - Adverse Drug Reaction Committee

B

BD - Bureau of Drugs
BSC - Board of Scientific Counselors (DCT/NCI)

C

CCOP - Community Clinical Oncology Program
CDC - Centers for Disease Control
CFR - Code of Federal Regulations
CIB - Clinical Investigations Branch (CTEP/DCT/NCI)
CTEP - Cancer Therapy Evaluation Program
CTEP-IS - Cancer Therapy Evaluation Program Information Service
CTMS - Clinical Trials Monitoring Service

D

DCT - Division of Cancer Treatment
DMF - Drug Master File
DN - Decision Network

F

FDA - Food and Drug Administration
FD 1571 - Notice of Claimed Investigational Exemption for a New Drug
FD 1573 - Statement of Investigator

I

IDB - Investigational Drug Branch (CTEP/DCT/NCI)
IND - Investigational New Drug Application
IRB - Institutional Review Board

M

MeCCNU (Methyl CCNU) - 1-(2-Chlorethyl)-3-(4-methylcyclohexyl)-1-nitrosourea
MOU - Memorandum of Understanding
5-MTHHF - 5-Methyltetrahydrohomofolate

N

NCI - National Cancer Institute
NDA - New Drug Application
NIH - National Institutes of Health
NIMH - National Institute of Mental Health
NLM - National Library of Medicine

O

OASH - Office of the Assistant Secretary for Health
OHRST - Office of Health Research Statistics and Technology
OPRR - Office of Protection from Rasearch Risks

P

PHS - Public Health Service
PRB - Pharmaceutical Resources Branch (CTEP/DCT/NCI)

Table Of Contents

Page

I. Introduction. 1

II. Cytotoxic Drugs - Background. 4

III. A Review of Two Cases Concerning NCI's Anticancer Drug Program Specific IND Cases. 8

IV. Memorandum of Understanding 11

V. Toxicology Protocol 12

VI. Clinical Trials 14

VII. New Drug Distribution and Investigators 20

VIII. NCI Investigator-Sponsor Roles: An Alternative 23

IX. Adverse Drug Reactions. 25

X. Therapeutic Intent. 27

XI. Protection of Human Subjects. 29

XII. Comparison of FDA-NCI Relationships with FDA - Industry Relationships. 32

XIII. Communication Problems 36

XIV. Sanctions. 39

XV. Summary. 40

Appendix A - Organizational Charts

Appendix B - Personnel Interviewed by the Task Force

Appendix C - Chronological List of Task Force Meetings

[illegible] ON AN[illegible]
NATIONAL CANCER INSTITUTE'S [illegible]D
THE FOOD AND DRUG ADMINISTRATION'S REGULATION

I. INTRODUCTION

On October 2, 1981, Dr. Edward N. Brandt, Jr., Assistant Secretary for Health, Department of Health and Human Services, established a Task Force on investigational new drugs to assess the National Cancer Institute's (NCI) anticancer drug development program institutional management systems and the Food and Drug Administration's (FDA) regulation of these anticancer drugs.

The Task Force was formed at a time when much Congressional and public media attention had been drawn to NCI's cytotoxic drug development program and the investigational new drug process. A series of Congressional hearings that highlighted issues included-

> On April 1, 1981, Representative Albert Gore, Jr., Chairman of the Subcommittee on Investigations and Oversight of the United States House of Representatives' Committee on Science and Technology, held hearings concerning ethical and institutional problems in biomedical research.
>
> On May 21, 1981, Senator Paula Hawkins chaired a hearing of the Subcommittee on Investigations and General Oversight of the United States Senate Labor and Human Resources Committee on oversight of the National Cancer Program and the last 10 years of progress toward a cure for cancer.
>
> On June 2, 1981, the full Senate Labor and Human Resources Committee, chaired by Senator Orrin Hatch, met concerning NCI contracting procedures.
>
> In late October and early November 1981, hearings were held in the House and in the Senate regarding the investigational new drug process and related issues. Particular areas of concern were protection of human subjects, public accountability for the testing of specific drugs such as MeCCNU, adverse drug reaction (ADR) reporting, and the relationships between NCI and FDA.

The charges in the press and testimony at the hearings highlighted a number of issues concerning NCI and FDA. The alleged problems were to be looked at against a background of new management of NCI and numerous important changes instituted over the past few years.

[illegible] Task Force: "(1) [illegible] NCI [illegible] monitoring [illegible] Investigational New Drug Application]; (2) to assess [illegible] review of NCI activities relative to these drugs; and (3) to develop recommendations for improvement that may stem from the findings of the Task Force."

The Task Force structured its study to examine the investigational new drug process for cytotoxic drugs from drug identification through toxicological and clinical evaluation of a drug to the point of availability to the cancer patient. Therapeutic intent, informed consent, ADRs, monitoring, accountability, and drug control are areas of concern as a new drug moves through the several stages of its development and evaluation. These critical areas of concern were examined in relationship to the several steps in the drug development and evaluation process.

The Task Force efforts were directed, for the most part, to cytotoxic drugs, although, for several issues, the problems were generic in nature, and cytotoxic drugs reflected broader drug development and testing problems.

The focus of the work was on the Division of Cancer Treatment (DCT) in NCI and the Bureau of Drugs (BD) in FDA, although others in NCI, National Institutes of Health (NIH), and FDA were consulted. Organizational charts for FDA and NCI are found in Appendix A. The Task Force members believed that views of investigators, institutional review board (IRB) members, and industry representatives would have been valuable if there had been additional time.

Ninety days was a short interval in which to address the numerous issues that were associated with the Task Force mission. An exhaustive investigation of all data presented to resolve discrepancies or to explore implications and perceptions given by interviewees was not possible. Because of the many facets of the cytotoxic drug program to be examined, the Task Force was composed of members from many different fields and disciplines; the advantage of diversity of views thereby gained necessarily balanced against the limited depth of expertise in the individual substantive areas considered. A deliberate decision was made to exclude persons who have ever had assignments in the cytotoxic drug development area.

Method of Work

Task Force members met with numerous interviewees, both in large Task Force meetings and in smaller groups, to gain understanding of the problems and issues and to obtain the many and often divergent views found among NCI and FDA staff. A list of those interviewed is found in Appendix B. In some instances, interviewees met with the Task Force several times. Interviewees were provided with the charge to the Task Force, a list of Task Force members, and opportunity for prior discussion with staff about expectations in the interviews. A list of Task Force meetings and discussions is included in Appendix C. No verbatim transcripts or recordings of the meetings with the Task Force were made. Summary minutes were kept.

Members reviewed documents, including hearing records and transcripts; memoranda; INDs, records, and letters in the files of NCI and FDA; minutes of meetings; staffing charts; mission and function statements of organizations and public advisory committees concerned with the investigational new drug development process; summaries and suggestions prepared by individual interviewees; newspaper articles; publications in scientific and professional journals; the Memorandum of Understanding (MOU) between FDA and NCI; the Drug Master File (DMF) of NCI; regulations; guidelines; laws pertinent to the investigational new drug development process; operational manuals; draft materials relating to new processes being established; reports of various commissions and other Task Forces -- past and current; contracts and requests for proposals; and investigational reports of FDA, General Accounting Office, and the Department of Health and Human Services (HHS), Inspector General. The group also considered descriptions, special analyses of raw data, and flow charts assembled by NCI and FDA staff. In addition, several cases were studied to elucidate concerns about reported lack of accountability; gaps in communication; ambiguity about roles and responsibilities of institutions, institutional review boards (IRBs), NCI investigators, and FDA staff; therapeutic intent; and sanctions.

The general findings and recommendations of the Task Force are presented in Volume I; more detailed background, discussion, and rationale for the findings and recommendations are presented in Volume II.

II. CYTOTOXIC DRUGS--BACKGROUND

Biology of Cytotoxic Drug Treatment of Cancer

A cancer cell differs from a normal host cell in important ways. Host defense mechanisms that are mobilized to repel or destroy an invading parasite of another species do not control cancer. Rather, the host nourishes and protects the malignant cells until, as a result of their uncontrolled multiplication, the host is overwhelmed and dies. In the present state-of-the-art, the approach to saving the host from cancer is to remove the cancer physically, or to kill every cell of a malignancy that has spread and cannot be treated locally.

Most drugs have their effects by chemically modifying some physiologic process in the host and producing reversible modifications that will disappear in time if the drug is withdrawn; in contrast, the essence of cancer chemotherapy is to identify chemical or other natural substances which destroy tumor cells (i.e., that are cytotoxic). Since cytotoxic drugs affect both normal and tumor cells, the goal is to identify compounds which are selectively more toxic for tumor cells than for normal host cells. The special value of cytotoxic drugs lies in their ability to reach all areas of the body, where they can come in contact with and possibly destroy discrete cancer cells which have spread from the obvious local tumor site. The role of cytotoxic drug treatment is often adjunctive to surgical or radiation therapy which is directed at local tumors. In more disseminated processes (e.g., leukemia), cytotoxic drug therapy becomes the prime mode of treatment.

Historical Development of Cytotoxic Drug Treatment of Cancer

In 1900, few patients with serious cancer were cured. Since then, the introduction of surgical resection and radiation treatment has provided increased rates of cure and palliation. Advances in surgical technique and radiation equipment and procedures, as well as in the supporting areas of anesthesia, blood transfusions, and antibiotics, have greatly augmented the extent to which surgical and radiation techniques have been applied successfully. Failure of further improvement in cure rates was due to continued growth of "micrometasteses"; that is, the growth of small groups of tumor cells that could not be recognized as having already spread beyond the local treatment site. Broad systemic treatment to reach such metastases was recognized as needed to supplement removal of a localized tumor. Following the models of successful use of antibiotics and systemic antimalarial drugs, a program was started to develop chemicals which might reach and control cancer cells wherever they were located in the body.

The discovery in the 1940's and 1950's of two chemicals with some antitumor effect (nitrogen mustard and methotrexate) led the U.S. Congress in 1955 to authorize the NCI cytotoxic drug development program. By 1970, it had been proved that drugs could, by themselves, cure patients with metastatic cancer. Since then, effort has been devoted largely to developing new cancer-combating drugs and testing their efficacy and safety.

Contribution of Cytotoxic Drugs to Treatment Results

There are now many types of malignancies that can be cured with drugs. Based on 1977 data, NCI staff estimates that 700,000 patients are found to have the more serious cancers yearly in the United States. Of 500,000 patients with "apparently localized" disease, 280,000 could be expected to remain free of tumor with use of either surgery or radiotherapy alone; the remaining 220,000 patients would develop recurrent tumors presumably from unrecognized spread to other body sites that had already occurred at the time of local treatment. This important group of 220,000 patients should, if identified, potentially benefit from cytotoxic drug therapy. Of the 200,000 patients who present with metastatic disease, about 92,000 will benefit to some extent from chemotherapy. It is estimated that about 46,000 patients per year are cured or have significant benefit from cancer chemotherapy.

The Cytotoxic Drug Development Program of NCI

In spite of the massive dimensions of the cancer problem in America, cytotoxic antineoplastic drugs have not been widely developed and marketed by the pharmaceutical companies (and hence are in the "orphan" category for the most part). Those that are clinically active may be superseded rapidly by newer drugs. There are over 100 recognizably different types of cancer; and a drug that is active in one type may be useless in all other cancers. Therefore, the market potential of any single drug is likely to remain small. These factors have made anticancer drug development unattractive to private industry and have led the American people, through Congress, to mandate this as a publically supported venture through NCI.

For the past 25 years, the NCI cytotoxic drug development program has encompassed a wide range of activities -- from identification of potentially useful materials to bringing them through clinical testing and into general medical practice.

NCI has developed a detailed Decision Network (DN) for moving a candidate anticancer agent from the initial identification stage through clinical evaluation. The steps in this complicated process, and those responsible for each, are presented in Figure 1.

The Screening Program

Drug development begins with the selection and acquisition of a wide variety of agents for screening studies to identify their activity by testing in panels of experimental animal tumors and human tumor tissues. There are two parts to the screening process; a "prescreen" testing of compounds in one mouse model, and, for those compounds which pass, a more elaborate and extensive "screen" in which the drug is tested in a panel of several mouse tumors. If found to be active against experimental tumors, the materials undergo large scale production and formulation both for detailed toxicologic studies in animals and for therapeutic clinical trials.

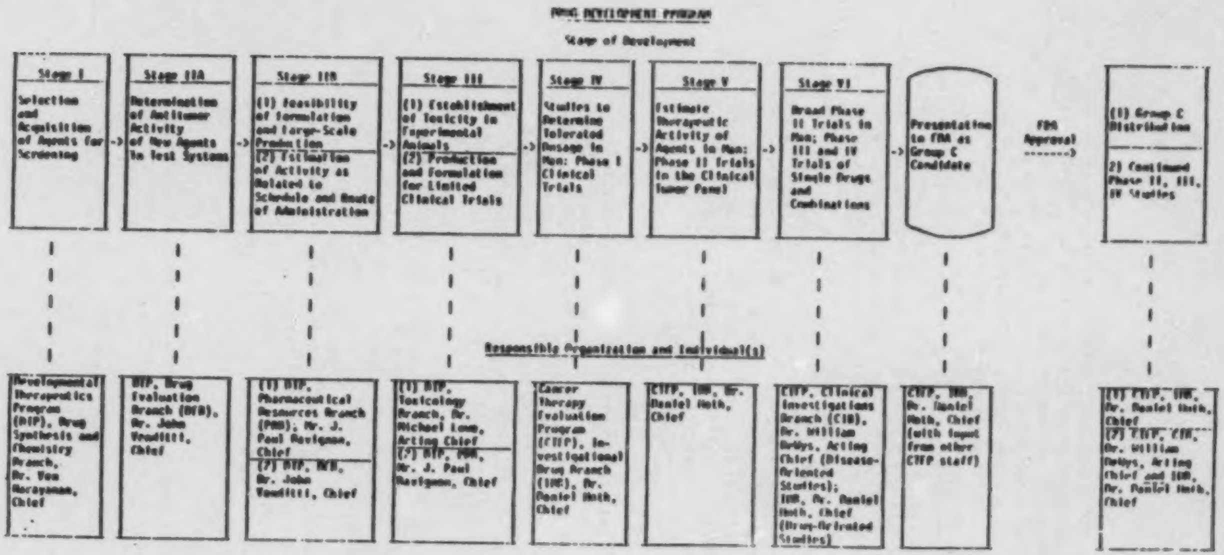

DRUG DEVELOPMENT PROGRAM
Stage of Development
Stage I
Selection and Acquisition of Agents for Screening
Stage IIA
Determination of Antitumor Activity of New Agents in Test Systems
Stage IIB
(1) Feasibility of Formulation and Large-Scale Production
(2) Estimation of Activity as Related to Schedule and Route of Administration
Stage III
(1) Establishment of Toxicity in Experimental Animals
(2) Production and Formulation for Limited Clinical Trials
Stage IV
Studies to Determine Tolerated Dosage in Man: Phase I Clinical Trials
Stage V
Estimate Therapeutic Activity of Agents in Man: Phase II Trials in the Clinical Tumor Panel
Stage VI
Broad Phase II Trials in Man; Phase III and IV Trials of Single Drugs and Combinations
Presentation to FDA as Group C Candidate
FDA Approval
(1) Group C Distribution
2) Continued Phase II, III, IV Studies
Responsible Organization and Individual(s)
Developmental Therapeutics Program (DTP), Drug Synthesis and Chemistry Branch, Dr. Ven Narayanan, Chief
DTP, Drug Evaluation Branch (DEB), Dr. John Venditti, Chief
(1) DTP, Pharmaceutical Resources Branch (PRB); Mr. J. Paul Davignon, Chief
(2) DTP, DEB, Dr. John Venditti, Chief
(1) DTP, Toxicology Branch, Dr. Michael Lowe, Acting Chief
(2) DTP, PRB, Mr. J. Paul Davignon, Chief
Cancer Therapy Evaluation Program (CTEP), Investigational Drug Branch (IDB), Dr. Daniel Hoth, Chief
CTEP, IDB, Dr. Daniel Hoth, Chief
CTEP, Clinical Investigations Branch (CIB), Dr. William DeWys, Acting Chief (Disease-Oriented Studies); IDB, Dr. Daniel Hoth, Chief (Drug-Oriented Studies)
CTEP, IDB, Dr. Daniel Hoth, Chief (with input from other CTEP staff)
(1) CTEP, IDB, Dr. Daniel Hoth, Chief
(2) CTEP, CIB, Dr. William DeWys, Acting Chief and IDB, Dr. Daniel Hoth, Chief

Figure 1

National Cancer Institute Drug Development Program

NCI
12/81

From 1955 to 1975, a total of 250,000 compounds, selected primarily by an empirical process were screened. A maximum of approximately 40,000 were screened in 1974. Following a change in screening approach in 1975, the number of compounds was reduced to approximately 15,000 annually. The prescreening program goal was to reduce the 15,000 to between 500 to 1,000 compounds per year which are then submitted to the broader animal tumor panel for evaluation. In 1981 approximately 12,500 compounds were screened. In 1975, NCI characterized its drug development program explicitly as a series of experiments to develop a system which would be more effective and efficient in identifying drugs useful in treating human cancer. Another part of the drug development program experiment is to explore in vitro tests that may predict human toxicity and therapeutic effect.

Toxicity Testing

For those drugs that pass the screening process, studies on toxicity follow. The purposes of animal testing are to identify a safe initial dose for humans, to identify types of toxicity that might be expected to occur in humans, to determine whether cumulative toxicity might be expected from repeated doses, and to assess whether toxicities are reversible.

The Clinical Testing Program

An extensive nationwide clinical testing program for cytotoxic drugs is sponsored and supported by NCI. Phases I, II, and III, the usual subdivisions of drug testing, are approached differently for cytotoxic drugs from other classes of drugs because of the special nature of their toxicity and the severity of the disease (Figure 1). For each drug that reaches clinical testing, studies of its effectiveness are sought in at least six different major tumor panels. Often drugs are tested in some of the other more than 100 different tumors.

For purposes of distribution by NCI for clinical testing, investigational new drugs are also classified as belonging to Group A, B, or C. These categories relate to specific development objectives and distribution procedures. Group A includes drugs in Phase I clinical trials and Phase II clinical trials in specified signal tumors. Group B includes drugs which showed promising tumor response rates in initial Phase II studies. Group C includes drugs that have demonstrated efficacy within a tumor type in more than one study, that alter the pattern of care of the disease in question. and that are safely administered by properly trained physicians without requiring specialized supportive care facilities. Drug C use is primarily for treatment purposes.

Drugs are distributed to investigators according to the kinds of studies they perform. The current Cytotoxic Drug Distribution and Cancer Treatment Plan is illustrated in Figure 2. Briefly, Phase I and early Phase II studies are restricted to Phase I Working Group Members (primarily Phase I contractors and NCI intramural investigators). When a drug is ready for wider Phase II

FLOW SHEET
CLINICAL CANCER TREATMENT
1981

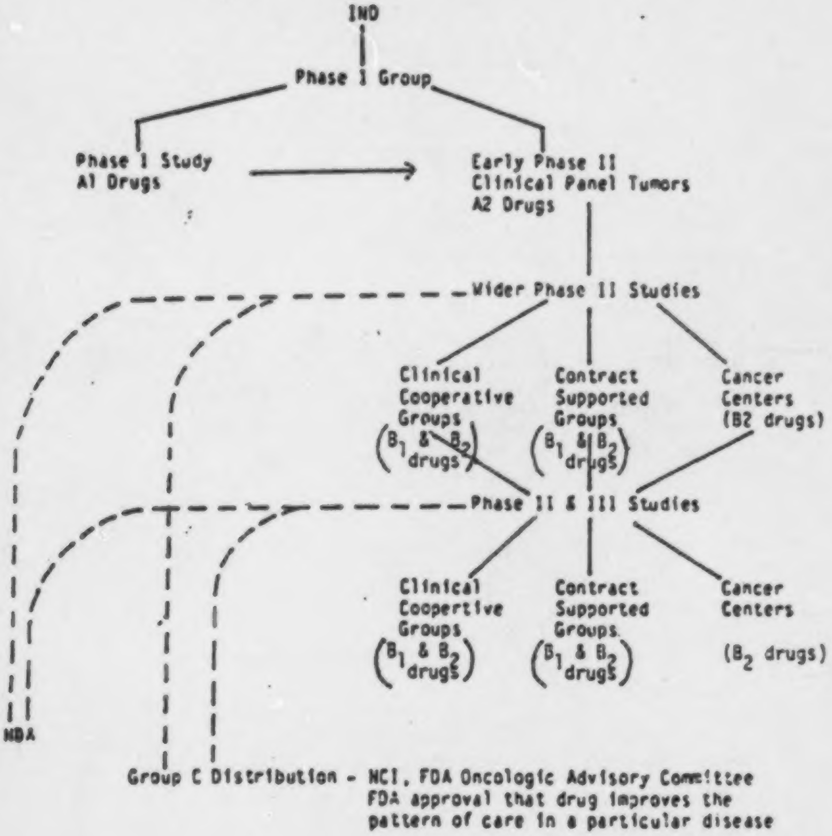

IND
Phase I Group
Phase I Study
A1 Drugs
Early Phase II
Clinical Panel Tumors
A2 Drugs
Wider Phase II Studies
Clinical
Cooperative
Groups
(B_1 & B_2 drugs)
Contract
Supported
Groups
(B_1 & B_2 drugs)
Cancer
Centers
(B2 drugs)
Phase II & III Studies
Clinical
Coopertive
Groups
(B_1 & B_2 drugs)
Contract
Supported
Groups
(B_1 & B_2 drugs)
Cancer
Centers
(B_2 drugs)
NDA
Group C Distribution - NCI, FDA Oncologic Advisory Committee
FDA approval that drug improves the
pattern of care in a particular disease

Figure 2. Current Cytotoxic Drug Distribution and Cancer Treatment Plan

NCI
12/81

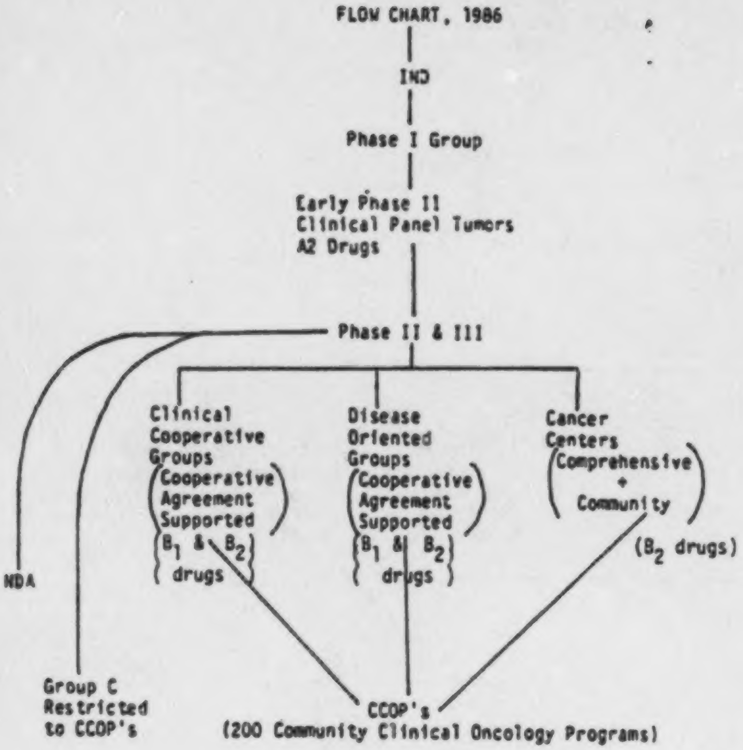

FLOW CHART, 1986
IND
Phase I Group
Early Phase II
Clinical Panel Tumors
A2 Drugs
Phase II & III
Clinical
Cooperative
Groups
(Cooperative
Agreement
Supported)
{B1 & B2
drugs}
Disease
Oriented
Groups
(Cooperative
Agreement
Supported)
{B1 & B2
drugs}
Cancer
Centers
(Comprehensive
+
Community)
(B2 drugs)
NDA
Group C
Restricted
to CCOP's
CCOP's
(200 Community Clinical Oncology Programs)

Figure 3

Figure 3. Planned 1986 Cytotoxic Drug Distribution and Cancer Treatment Plan

NCI
12/81

and III studies, it is made available to the clinical cooperative groups, the contract-supported disease-oriented groups, and the cancer centers. When a drug is approved by FDA for Group C, it is also made available with guidelines for use to individual physicians who have filed registration form FD 1573, Statement of Investigator, with NCI.

The future NCI drug distribution and cancer treatment plan is indicated in Figure 3. No major changes are planned in the distribution of drugs for Phase I and early Phase II studies. The major differences projected for 1986 relate to the institutions that will be involved in the proposed Community Clinical Oncology Program (CCOP). Plans are to eliminate distribution of Group C drugs to individual physicians and to utilize instead the CCOP investigators. The CCOP institutions will participate in certain Phase II and III studies with the cooperative groups, centers, and so on.

Current Scope of NCI Cytotoxic Drug Development Program

The NCI is presently sponsor for about 70 active cytotoxic drug INDs which are in various stages of clinical testing. Because cancer constitutes more than 100 biologically different tumors, individual cytotoxic drugs often are in different stages of testing simultaneously for more than one kind of tumor.

Twenty-nine cytotoxic drugs have been marketed for treatment of cancer. NCI has played an important role in the research and development of 19 of these anticancer drugs. The scope of the NCI effort is illustrated by the facts that only one of 5,000 compounds screened reaches the stage of clinical evaluation and only one of 50,000 drugs screened in animals for anticancer activity reaches the cancer patient through the market place. Between 1975 and 1981, 30 INDs were opened for cytotoxic drugs, and one inactive IND was reopened.

Eight drugs have been or are in the process of being tested in all the panel tumors (Leukemia, Lymphoma, Lung, Breast, Colon, and Melanoma). Five additional drugs have been tested in five of the six tumor panels. Also, 11 have been tested in tumors other than the panel. The most frequent "nonpanel tumors" tested have been sarcomas, and ovarian, renal, and brain tumors.

III. A REVIEW OF TWO CASES CONCERNING NCI'S ANTICANCER DRUG PROGRAM

A number of cases came to the Task Force's attention in which it was alleged that researchers and/or administrators acted improperly in carrying out their responsibilities under the NCI drug development program. These cases do not themselves prove that there are deficiencies in the program. They at least raise questions, however, as to whether there are shortcomings that need to be addressed in such areas as approval of new protocols; reporting of ADRs in ongoing protocols; training of researchers and administrators; monitoring of researchers by NCI, FDA, and institutions; protection of human subjects; and control of drug distribution.

To assist in carrying out its charge, the Task Force examined a number of cases aired in Congressional hearings on NCI's drug development program. In so doing, the Task Force did not consider it necessary, nor did it have the detailed information or time, to resolve factual disputes or develop definitive chronologies. The Task Force recognized the difficulty in generalizing from individual incidents which might simply reflect isolated aberrations rather than fundamental problems. Nevertheless, the Task Force considered these cases as important guideposts in identifying areas of the drug development program to be scrutinized and evaluated. Furthermore, the extensive interviews heard by the Task Force have indicated that the preceding problems encountered in the cases are not isolated.

Without attempting to catalog each case, two deserve specific mention because they not only have been widely publicized, but because they point up most of the issues raised by the entire range of specific situations that have come to the Task Force's attention.

Methyl CCNU and Renal Insufficiency

As far as the Task Force can determine from the information supplied to it, Methyl CCNU (MeCCNU) was an anticancer drug developed by NCI in the late 1960's. Preclinical studies in monkeys and dogs showed the drug caused acute renal insufficiency. In 1971, NCI filed an IND with FDA and began Phase I trials with MeCCNU. At that time, NCI distributed a brochure to investigators which recounted the results of the animal studies. It is not clear whether or not this information was passed on by investigators to their patients. Phase I trials were completed by early 1972 with no evidence of renal insufficiency being noted. During the next 6 years, the drug proceeded through a series of Phases II and III trials, again with no renal insufficiency being noted. In 1976, with the approval of FDA, NCI made MeCCNU available for wider distribution and use in treating various forms of cancer. In August 1977, NCI received a report of renal damage in a 5-year-old child who had been on the medication for 17 months.*

---

* Task Force members were advised of possible reports of renal insufficiency prior to this time, but were unable to confirm whether such reports actually occurred and, if so, to whom they were made.

Several more cases of chronic renal insufficiency in children were reported in mid-1978. At that time, NCI decided to study the matter further before contacting FDA, to ensure that the renal insufficiency was indeed related to MeCCNU. To make this assessment, NCI contacted all its investigators using the drug for the purpose of seeking further information. As a result, in late 1978, a number of added cases were discovered. This led NCI's Adverse Drug Reaction Committee (ADRC) to conclude in February 1979 that the renal insufficiency was associated with MeCCNU, and, almost immediately NCI filed an ADR report with FDA. NCI also then advised all investigators on the MeCCNU distribution list of these findings and requested reporting of any additional cases. In addition, NCI's MeCCNU protocol was amended to incorporate the findings. In July 1979, FDA inspectors conducted the first of several visits to NCI regarding MeCCNU. These contacts have led to modification in NCI procedures for reporting ADRs to FDA. No sanctions were imposed against investigators who failed to report ADRs to NCI in a timely manner.

5 Methyl THHF

In 1978, NCI supplied a scientist at M.D. Anderson Hospital with an experimental compound, 5 Methyltetrahydrohomofolate (5 MeTHHF), for use in animal pharmacology studies. Between March and July 1980, the scientist and his collaborators carried out clinical pharmacology studies on six patients using 5 MeTHHF. Although M.D. Anderson had received preliminary approval from NCI for such a study, it had not been approved by the M.D. Anderson IRB, nor did M.D. Anderson have an FDA-approved IND for the study. In late April 1981, the M.D. Anderson scientist presented the results of his study at a professional meeting. In mid-June 1981, the study came to the attention of NCI officials who immediately contacted FDA and sent a site visit team to M.D. Anderson. The team verified the facts and made a number of recommendations including the following: termination of the contract under which the study was conducted; recovery of federal funds used to support the study; modification of M.D. Anderson procedures to ensure better compliance with NIH and FDA requirements; and removal of the scientist from leadership responsibility for federally-supported research. These recommendations were adopted by the Director of NCI and NIH, with the added stipulations that for 2 years the scientist's infractions be brought to the attention of committees considering applications by him for NIH support, and that, for the same period, he not be allowed to serve on NIH advisory committees.

In themselves, these and other similar cases that have come to the Task Force's attention, do not prove that there are deficiencies in the NCI drug development program. They do, however, indicate failures in the specific instances involved which raise more general questions as to the adequacy of -

- procedures for reporting new clinical protocols and ADRs in ongoing clinical protocols;

- programs for training researchers and administrators as to their reporting responsibilities;

- monitoring of researchers by NCI, FDA, and their own institutions;
- procedures for ensuring that human subjects are protected;
- controls on distribution of experimental drugs;
- sanctions for failure to follow established procedures.

In subsequent sections in Volumes I and II, the Task Force will systematically examine the NCI drug development program as it exists today, identify strengths and weaknesses, and make recommendations for change. In so doing, the Task Force will attempt to be responsive to questions raised by the MeCCNU, 5 MeTHHF, and other specific cases. NCI and FDA, however, are aware that there have been shortcomings in the program, and they have already taken significant steps to alleviate them. It is hoped that, to the extent the individual cases referred to above reflect common problems in the program, the changes already instituted, plus such others as may be adopted in response to this report, will reduce the likelihood of similar cases occurring in the future.

IV. MEMORANDUM OF UNDERSTANDING

A Memorandum of Understanding (MOU) relative to anticancer drug development has been in effect between FDA and NCI since February 1979. The purpose of the MOU is to supplement and strengthen the ongoing direct but informal working relationship between FDA's BD and NCI's DCT. Primary responsibility for a cooperative liaison resides with the Director, DCT, and the Associate Director for New Drug Evaluation, BD. The MOU provides for information exchange and staff-to-staff liaison. Unresolved issues are to be elevated to higher authorities in each organization. The final resolution point is the Commissioner of Food and Drugs.

A major element in the MOU is the maintenance in BD of the NCI Drug Master File. The information contained in NCI's DMF is applicable to its INDs. Reference in the IND to the DMF material precludes the necessity of voluminous, redundant submissions. Although the April 1981 revision of the Toxicology Protocol in the DMF is accompanied by a letter providing an index to that section, the DMF has no overall index.

It is believed by the management of both organizations that the MOU has worked well. A recent review of the agreement by each organization did not bring forth any recommendations for change.

Staff perceptions of the efficacy of the cooperative liaison called for in the MOU are uneven. The problems, however, relate to the implementation of the MOU, not the document itself. The Task Force does not find a need for change in the MOU but concludes that the MOU is an appropriate document in which future management and operational statements may be incorporated in the attempt by NCI and FDA to maintain a sound and responsive program for anticancer development.

V. TOXICOLOGY PROTOCOL

The Toxicology Protocol has been revised through a long, thoughtful and open process which permitted the consideration and, in some instances, acceptance of dissenting views. The principal aim of the process of revision -- to provide a more streamlined Protocol for preclinical toxicity testing that reflects the accumulated knowledge of the utility of that testing -- seems largely to have been accomplished. The major part of the new Protocol appears to have the support of the great majority of the oncology community. The length and openness of the process have led to several problems, however, that have not yet been solved. The many changes that have been suggested and accepted, since NCI first proposed the new Toxicology Protocol in 1979 have resulted in there being no single document that all agree is the new Toxicology Protocol. As a result, there is considerable misunderstanding among FDA and NCI staff as to the details of the Protocol. As one example, the version of the Toxicology Protocol in the DMF as of December 14, 1981, did not specify how the results of animal testing will be used to determine the initial dose for humans. As a second, some FDA staff have criticized the new Protocol for its failure to include the determination of a dose-adverse response curve in dogs, but were not aware of the recent change that provided for escalating doses in dogs until frank toxicity is reached, a reversal of NCI's 1979 position. As a third, the criteria for determining when additional toxicity testing in animals will be required before starting human trials--required by Commissioner Hayes when he approved the new Protocol in October 1981--have not yet been formalized or included in the DMF.

The evoluntionary character of the new Toxicology Protocol is an expected and desirable quality, but the lag in that process lessens the credibility of formal approvals given at earlier stages of its development. FDA's Oncologic Drugs Advisory Committee approved in 1979 a version much different from that now in place or proposed. For example, their Toxicology Guidelines Subcommittee directed that animals that had not yet recovered from the acute effects of toxicity experiments should not be killed, but rather be observed to see whether the toxicity was reversible; whereas, the present version of the Protocol does not permit continuing observation of mice and makes such observation of dogs optional.

Despite these problems, a protocol appears to have been agreed to which, in large part, seems to reflect fairly the state of understanding of the usefulness of preclinical toxicity testing and which accommodates the most persuasive arguments of its earliers critics. Further, there is no difference in the manner in which industry or NCI would be treated with regard to this class of drugs; all aspects of the Toxicology Protocol used by NCI sponsorship of INDs could also be used by industry upon request. There is the need now to write down all that has been agreed to and to seek a grand round of approval -- including approval from those who have previously given it. The FDA proposal to publish the Protocol in the Federal Register for general comment is reasonable, and the comments generated will provide additional information and perspectives that may aid the deliberations of the advisory committees.

Recommendations -

1. The value of the dog and mouse as predictors of qualitative toxicity, the value of dose escalations in dog in predicting cumulative toxicity, and the effectiveness of the proposed scheme for selecting a safe and efficient starting dose for humans should be reconsidered repeatedly in light of accumulating experience under the new Toxicology Protocol. A schedule for such reconsiderations should be drafted by NCI, as it would improve the chances that appropriate changes in the Protocol will be made promptly, and would enhance the credibility of this important scientific and medical document.

2. The updated new Toxicology Protocol -- including contingencies for nonroutine testing (such as testing for possible cumulative toxicity and performance of animal histopathology prior to human testing), a description of how the results will be used to calculate the initial dose for humans, and the planned schedule for analysis of accumulating results -- should be assembled and presented to the appropriate FDA and NCI advisory committees for approval.

VI. CLINICAL TRIALS

The apparatus which has been developed by NCI for the clinical testing of anticancer drugs is extensive, complex, and not free of redundancy. It includes contract investigators, cancer centers, cooperative groups, and satellite investigators who report to NCI only indirectly. Funding is made available through various types of grants, contracts, and the new instrument, the cooperative agreement. There is also a panoply of review and advisory committees whose functions and membership overlap to a varying degree. The extent to which investigator initiative is paramount in the design and execution of clinical studies also ranges widely between the possible extremes. The complexity of the system by which research is organized adds to the inherent complexity of evaluating cancer treatment. History has played an important role in the determination of the structure of the present system. It is continuing to evolve under pressures generated by proposed and promulgated FDA regulations on the one hand and community demand for effective drugs on the other, with NCI assuming an ever-increasing degree of initiative in designing drug trials and in controlling drug distribution.

Organization and Management by NCI

The Task Force has not been able to find any single, authoritative document that currently describes the totality of this system. Those that do exist and are an official part of the DMF, are not complete and up-to-date in all respects. NCI and FDA staff have varying degrees of familiarity with the system, but understanding of its structure and procedures is not uniform even within NCI. In part, this may be due to the large number of recent changes in key personnel, but it is a situation that should be corrected.

> Recommendation -
>
> NCI should develop and maintain a single, comprehensive, and up-dated description of its drug-testing organization, its procedural requirements, and the responsibilities of investigators. Copies of this document should be made available to all investigators, centers, cooperative groups, and so on, and utilized in an expanded educational effort.

One recurring criticism of NCI's clinical trials, which appears to the Task Force to have justification, is that too many patients are enrolled in some Phase I and Phase II studies, even in those studies whose results to date have been consistently negative; while other Phase II protocols, which might yield useful information, are not being completed in a timely manner. This problem should be relatively easy to rectify by focussing attention on the determination of sample size in clinical trial protocols and enforcing adherence to the approved protocol during its execution.

Recommendations -

1. NCI should require that every protocol include a clear statement of the number of patients to be studied as a condition for approval and that a proposal to amend the number be approved by the appropriate IRB(s) and NCI committee(s).

2. Each protocol should also show how patient accrual will be monitored as execution of the study begins and how accrual will be stopped when the approved sample size has been achieved.

3. The quantity of drug that will be required to complete the approved protocol should be estimated at the outset, and the cumulative amount shipped under that protocol number should not be allowed to exceed the estimate without an explanation and a check on total patient accrual.

The Task Force believes that at this time no scientifically sound basis exists for making a decision to abandon further Phase II testing against additional types of cancer, when results with a number of common types have proved negative. The fact that drugs exist which favorably affect only one or a few uncommon types of cancer argues against the adoption of any rigid stopping rule; yet, common sense suggests that a drug which has been repeatedly tested with no response observed need not be fully tested on each and every one of the pathologically differentiable types of cancer. As data accumulate from the completion of progressively more Phase II studies, with both the number of drugs and the number of tumors that have been tested continuously increasing, NCI has the opportunity to define patterns of association, if such exist.

Recommendations -

1. NCI should conduct analyses of treatment results at appropriate intervals to define the degree to which the effectiveness of a drug in one tumor affects the probability of effectiveness in another tumor, and the results should be incorporated into the decision process that assigns priorities to Phase II protocols.

2. NCI's IDB should take a position of clearly understood leadership in the execution of the requisite number of Phase II drug tests on varying types of cancer, so that initial determination of the possible clinical efficacy of a drug will not be long delayed after the completion of Phase I. This recommendation includes the negotiation of additional clinical testing contracts, if necessary.

An elaborate network of chartered advisory groups oversees the drug development efforts of NCI, but most of the critical operating decisions are made by CTEP staff members and clinical investigators. Reports of the meetings of these inhouse committees are widely distributed, but they do not include enough information about the substance and procedures used to permit judgment of the functioning of the committees. This leads, in turn, to difficulties in explicating and evaluating the research strategy used in the clinical testing program.

Recommendation -

> NCI should conduct a systematic analysis of the timeliness and appropriateness of the key decisions made by staff review groups such as the Protocol Review and DN Committees.

The purpose of this retrospective review would be to assist in the formulation and testing of more explicit decision rules and criteria. The study would search for any patterns and possible sources of errors and omissions in the information available to the decision makers as well as any apparent biases or inconsistencies in the decisions reached. This study should provide evidence to confirm or refute the impression that decisions are arrived at in an arbitrary or capricious manner and charges that NCI staff are reluctant to challenge the activities of prestigious investigators. It should also lead to better specification of the information needed at each point in the decision process.

In view of the central role occupied by the IDB and the Clinical Investigations Branch (CIB) in anticancer drug development, the Task Force believes that an annual overview of the work of these branches should be presented to an advisory committee composed of reviewers who are not NCI staff. This review should include a presentation of IDB and CIB policies, practices, and procedures in such areas as clinical trials monitoring, patient accrual, informed consent form review, drug distribution system, ADRs, interface with FDA, and relationships of IDB and CIB to the total DCT program. The DCT Board of Scientific Counselors (BSC) could serve as the appropriate review committee. An annual report to the Directors of DCT and NCI would reflect oversight activities on the progress, difficulties, and direction of these branches.

NCI staff have proposed developing a computerized Cancer Therapy Evaluation Program Information System (CTEP-IS) to provide scientific and administrative information on treatment modalities, diseases, protocols, and investigator teams. The system would abstract information from protocols and status reports reviewed by the various CTEP branches, and provide cross references to existing data about drugs and investigators. The system would produce periodic reports on topics such as - (1) administrative status of investigational drugs; (2) administrative status of all protocols in the review process; (3) background information to assist in protocol reviews, such as related ongoing studies and the impact of the protocol on drug inventories and drug use rates; (4) objectives and results of ongoing studies, organized by treatment modality, specific disease, phase of the study, and investigator; and (5) delinquent reports.

The proposed information system could compensate for the information deficits which result from the decentralized innovative investigator-initiated part of the NCI supported research program and might contribute meaningfully to the interim scientific program analyses and management decisions.

Monitoring of Clinical Trials by NCI

The Clinical Trials Monitoring Service (CTMS) provides, through a contract, for the rapid collection and summarization of data in Phase I and some Phase II studies. In addition, it conducts site visits to verify the data submitted by checking against independent sources and to monitor compliance with NCI and FDA requirements concerning, for example, documentation of informed consent and recording of drug distribution. A number of apparent discrepancies have been reported to NCI, including delays in submitting reports, and notable variations among investigators in percentages of patients on study who actually fulfill eligibility criteria.

Recommendations -

1. IDB should develop procedures for prompt review of the clinical and administrative data problems, and findings of CTMS, for implementing corrective action with investigators, institutions, or cancer cooperative groups, and for monitoring of the effects of such action upon the performance of the clinical trials.

2. NCI should strengthen its clinical trials management activity promptly, to add management oversight and enforcement capabilities to the current monitoring effort. This management group should be given responsibility for ensuring that researchers using investigational drugs under NCI sponsorship comply with approved study protocols, drug distribution policies, and ADR reporting procedures, as well as the requirements for annual reports, informed consent, and good laboratory practces. The activity can provide the information needed by NCI and its advisory committees to evaluate the success of the current research strategy and to compare it with modified or alternate approaches.

3. NCI should examine the extent to which the clinical, laboratory, and pharmaceutical record systems can be linked and reconciled (through standardized records or even through computer coupling) with the drug distribution management system and the clinical trials information system. This would enhance NCI capability to facilitate the tabulation and analysis of data to support a later NDA; and to develop more systematic and efficient investigative and auditing practices, more effective management, and more complete and timely reporting.

NCI regards the CTMS as experimental and believes that the need for its continuation should be evaluated after it has functioned for an appropriate period of time. Some members of the Task Force agree, while others believe that such on-site data verification and compliance monitoring are already clearly needed in at least Phases I and II studies performed under NCI's INDs. The Task Force members all agree that if the results of the evaluation of CTMS reveal widespread substantive deficiencies, not only should attempts be made by IDB to correct these deficiencies, but also serious consideration should be given to examining the quality of data in other NCI-sponsored clinical drug testing.

FDA Monitoring of NCI's INDs

In its regulatory role, FDA reviews NCI's interim analysis processes via NCI's submitted annual reports, clinical protocols, and minutes of working groups, cooperative study groups, and so on. There has not been any evidence presented that FDA's review of the NCI interim analysis process is less than that for industry's cytotoxic drug efforts; indeed, the extra communication channels established between NCI and FDA probably give FDA opportunity for greater insight into NCI's IND process and for enhanced oversight of NCI than of industry cytotoxic drug interim analyses. FDA conducts less data verification of cytotoxic drug investigators than others because of a policy that emphasizes audit of those drugs with pending NDAs.

Recommendation -

BD should include all of the NCI-sponsored drug investigators within their selection procedures of investigators and institutions for review on a routine basis. To the extent possible, FDA should utilize the results of NCI monitoring to minimize duplication and to utilize FDA inspectors in the regions to conduct the monitoring as is done for other drug monitoring.

Investigator Responsibilities

The investigators conducting IND studies have many responsibilities resulting from their multifaceted roles as physicians, research scientists, and clinical investigators. The responsibilities of clinical investigators for INDs are to ensure (1) adequate protection for the rights and safety of subjects involved in clinical studies, and (2) the quality and integrity of the resulting data submitted to the sponsor.

Each investigator must submit a protocol to NCI which has been approved by the local IRB. The investigator must maintain records which include clinical observations and laboratory data as required by the protocol about each patient entered on a research protocol. Reports of the study must be submitted to NCI on a periodic basis. The frequency of these reports varies with the phase of study and the type of support mechanism. For Phase I studies, reports are submitted to NCI on every patient every 2 weeks. For other phases, conducted through cooperative groups, reports are submitted to the cooperative group statistical office two or three times a year, and each cooperative group supplies NCI with a report of its studies on a twice per year basis. Institutions performing Phase II/III studies under cooperative group aegis report to NCI annually. The terms of these reporting requirements are contained in the documents supporting the funding mechanism, i.e., either the contract or the cooperative agreement. Each investigator is required to comply with all relevant rules and regulations about obtaining informed consent. Furthermore, each investigator is required to provide to NCI reports of ADRs and to comply with NCI ADR policy (see section on Adverse Drug Reactions). Each investigator is required to provide NCI with a summary report of the study shortly after its completion. The above requirements conform, in general, to the stipulations in form FD 1573 which every investigator using NCI investigational drugs has signed.

VII. NEW DRUG DISTRIBUTION AND INVESTIGATORS

The clinical trials research program testing cytotoxic investigational new drugs is complex and continually evolving. Each year over 5,000 clinical investigators administer approximately 70 investigational anticancer drugs (40 under intensive investigation). Approximately 37,000 new cancer patients enter NCI clinical trials each year. These drugs are given to treat patients and to determine safety and efficacy of the drugs and the future role of the drugs in total patient care.

These investigators qualify for use of drugs categorized in three drug distribution groups, A, B, and C, based on the kind and extent of clinical studies they are conducting under NCI sponsorship.

Group A drugs are available only to a small group of select investigators, called the Phase I-II Working Group, who conduct the basic Phase I and Phase II studies to establish a safe dosage schedule and the magnitude of effectiveness of the drug for specific tumors. These early drug studies in small numbers of patients are prerequisites for further large-scale testing. The investigators conducting these drug-focussed studies are oncologists with additional expertise in clinical pharmacology.

Group B drugs are available to much larger and more diverse group of investigators conducting primarily disease-focussed studies using drugs which have demonstrated safety and have had a significant response in specific tumors. These are mostly late Phase II and Phase III trials of combinations of the new drug and marketed drugs, radiotherapy, and surgery comparing the efficacy of differing therapeutic plans to determine the role of the new drug in treatment of the disease.

Group C drugs are investigational new drugs which NCI staff and FDA's Oncology Advisory Committee have approved for wider distribution prior to approval of an NDA permitting marketing. Group C makes the drugs available to physicians in the community who have registered on a form FD 1573, for treating individual cancer patients. A common protocol or "guidelines for clinical use" specifies the type of tumor to be treated and dose and dosage schedule to be used.

The Task Force was satisfied that NCI has a policy and procedures which ensure that drugs are being distributed directly only to investigators for valid purposes and that proper records and files of shipments are kept. The system can generate reports of all investigators who have received a given drug, the amount of drug a given investigator has received, and of all investigators working on a given protocol.

Recommendation -

NCI should require: (1) that all investigators including those affiliated investigators practicing in satellites of cooperative group institutions and cancer centers be formally registered by a form FD 1573 either as individual investigators or listed as under the personal supervision of the principal investigator and a specific IND number. (This information should be made available to FDA to permit inclusion of all NCI investigators using NCI supplied chemotherapy in its strategy for selecting investigators for routine investigations); (2) that all drugs provided under a specified protocol for human use but not used in accordance with that protocol be returned to NCI for proper handling by the Pharmaceutical Resources Branch (PRB), DCT, NCI; (3) that communication links about eligibility to receive drugs and drug usage be developed among PRB and the appropriate other branches of DCT to control drug distribution and leakage effectively; and, (4) that under circumstances of noncompliance with NCI's requirements or FDA's regulatory requirements, no cytotoxic drug be shipped from NCI to the investigator.

If the principal or clinical investigator is out of compliance with PRB requirements for anticancer drug control, PRB will be responsible for bringing the violation to the attention of the Director, DCT, for appropriate action.

Currently, investigators receive relatively little information from NCI about their responsibilities in handling the drug beyond that in the approved protocol and the requirements listed on the form FD 1573.

Recommendation -

NCI should develop a set of instructions or guidelines on drug-handling responsibilities of investigators to be sent out once a year to every investigator who files an updated or new form FD 1573.

NCI's ability to account for the distribution and use of a drug after it has been shipped is currently not satisfactory, but NCI has plans for remedying these deficiencies which will be implemented in early 1982. At the present time, there is a "return drug program and a recall program" to retrieve drugs at time of termination of INDs or individual protocols. There is, however, no way of documenting how unreturned drugs were actually used. In the plan to be implemented, investigators receiving drugs will be required to keep a detailed log showing the disposition of all medication received. This log would be "audited" at time of site visits by checking against clinical records to be sure the drug was used as recorded. Further, summary data from the log would be required to be submitted periodically to NCI where it would be stored on computer and the data used to check against investigators' progress reports. The computer record summary could be taken on site visits to be checked against the actual log. The proposed plan appears to be sound, reasonable, and likely to be effective.

Recommendation -

High priority should be given to implementing the proposed NCI plans as soon as possible to remedy what is viewed as a serious defect in the current drug distribution system. Requiring such logs and reporting should both dissuade investigators from misuse of drugs and readily identify

> the practice of "secondary" distribution of investigational drugs, that is, the transfer of drugs to physicians outside the regulated environment and the use of investigational drugs for unapproved purposes.

NCI has suggested that, in the future, distribution of Group C drugs will be restricted to the 200 CCOPs now being developed. This approach is likely to increase the concern of those who argue that NCI is using its drug distribution system to establish a controlled medical delivery system through the selection of a special group of physicians to receive new drugs. Another point of contention is the limited reporting required of physicians using Group C drugs; it is held that useful information about the efficacy and the limitations of these drugs is being lost because patients are "diverted" from protocol-directed studies, possibly delaying the accumulation of evidence needed to support an NDA. NCI feels that the Group C mechanism provides a means to respond to medical and public pressure for improving cancer therapy as quickly as possible without ignoring their responsibilities to ensure that physicians are sensitive to the risks in using these agents. NCI is also concerned about the problem of loss of information; staff will continue to encourage physicians to refer patients to study sites whenever possible and looks forward to the CCOP organizational structure as a way to reduce this loss.

Group C drug classification provides a useful mechanism for bringing these drugs which have demonstrated efficacy against a specific tumor type to the cancer patient on a wide basis.

Recommendation -

The Group C drug classification should be retained.

Investigational drugs that are not intended for human use have, on rare occasions, wrongly been given to patients without an IRB- or NCI- approved protocol and without FDA approval of an IND. The Task Force believes that such malfeasance cannot effectively be prevented by NCI by tighter control on the distribution of drugs for preclinical studies. It is much more practical to rely on education, clear labeling of materials not approved for human use, and significant disciplinary action in the case of willful violation of the law in this regard.

In summary, the anticancer drug distribution controls are adequate for the task of ensuring accountability. Drug leakage will be controlled by the procedures now being implemented by NCI. Further, the monitoring of investigators and institutional records will significantly increase the sensitivity and commitment of investigators to see that anticancer drugs are used for the intended protocol and that unused drugs will be returned properly and in a timely manner to PRB.

VIII. NCI-INVESTIGATOR SPONSOR ROLES: AN ALTERNATIVE

The Task Force discussed an alternative for implementing parts of the NCI-FDA cytotoxic drug development program.

NCI may be seen as having two distinct and important roles in the clinical trials research conducted with investigational new cytotoxic drugs. One role would be to provide the data base needed for a New Drug Application (NDA), IND studies directed to support NDA approval requirements. In this role, the comprehensive preclinical and clinical development of the drug would be carried out to determine the drug's safety and efficacy with the goal of making a safe and effective drug available to oncologists and their patients through the NDA process. The studies would encompass all preclinical screening and toxicity testing; all the basic Phase I and Phase II trials which establish a safe dosage schedule, the drug's toxicity and the magnitude of effectiveness for specific tumors; and finally, selected "pivotal" Phase III studies which definitively establish the safety, effectiveness, and role of the drug in the therapy of neoplastic disease in broader patient populations approximating future intended medical use.

The other role is to provide support for important field investigator-initiated clinical trials that are not a part of the NDA drug development thrust. In this role, the mission would be to develop drugs or combinations of drugs which are effective as programs of cancer treatment, with the focus on the treatment of a particular disease type rather than the detailed demonstration of the efficacy of a particular drug. These studies are currently performed in late Phase II and Phase III under NCI's INDs. NCI currently performs both roles which are under the regulation of FDA.

During the Task Force discussion, a different concept emerged that could (1) lead to more rapid drug development, submission, and approval of an NDA, and (2) free NCI from serving as IND sponsor to the non-NDA oriented, field investigator-initiated studies which comprise the vast majority of Phase III studies. NCI support and assistance to field investigators need not be diminished. Physicians in cooperative groups and cancer centers initiating and conducting these nonpivotal Phase III studies could serve as sponsor-investigators of their own INDs by filing directly with FDA. This approach would shift current NCI responsibilities as drug sponsor, especially detailed protocol monitoring, and ADR and progress reporting to the oncology treatment community itself for non-NDA directed studies. FDA would deal with these INDs as they do with other sponsor investigator-initiated IND studies.

NCI would continue to supply drugs for these studies and permit these investigators to reference NCI's IND for chemical, manufacturing, preclinical toxicity, and relative effectiveness data necessary for IND approval. In exchange for these services, NCI would continue to exercise the right to prior protocol approval before the drug is shipped and would continue to require annual progress reports. NCI would therefore have information on all ongoing trials with these drugs.

Other members of the Task Force had some reservations about these concepts, including -

1. Authority would be separated from responsibility. Relinquishing the IND sponsor role would take away some of the authority from NCI for obtaining responses from the investigators who would be holding their own INDs;

2. Responsibility for science/program interim analysis of results of clinical trials would, in large part, be shifted from NCI to FDA. Currently, NCI's capability for such monitoring exceeds that of FDA. This shift would lessen a much needed activity;

3. Clinical oncologists would receive less assistance from NCI in complying with regulatory requirements.

There is also a relationship between the two described roles and the Group C drug designation which needs to be addressed. The Group C distribution mechanism, serving as an "NCI institutionalized compassionate IND procedure," is endorsed. It is recognized, however, that this drug distribution mechanism is a deviation from and exception to the policy that all licensed physicians have the authority to prescribe "approved" drugs. Further, the criticism that Group C drugs are approved for broad distribution for treatment with less detailed evidence than required for NDA approved drugs cannot be contradicted as long as a different approval procedure is used by FDA. This valuable drug distribution mechanism was conceived to bridge the time gap between which efficacy and safety was demonstrated to the satisfaction of some, and an NDA was submitted and approved constituting the official mechanism for drug marketing and distribution. However, since NCI has not been highly successful in attracting commercial NDA sponsorship for a number of Group C drugs, the mechanism has been expensive to maintain while not productive from a research perspective, and has been seen by some as a permanent solution for distribution of some cytotoxic drugs. To remedy this situation, NCI should take the steps necessary to move drugs from Group C to NDA status as quickly as possible, e.g., conducting definitive NDA-oriented studies or serving as the NDA sponsor of last resort. If these steps are built into the planning of a drug's development, the additional cost to NCI to accomplish reaching NDA status may not be great. The feasibility of this approach requires additional consideration.

The Task Force is unwilling to take a position on the ultimate adoption of this alternative as it has not been able to evaluate all the extant evidence which might clarify the possible advantages and disadvantages.

IX. ADVERSE DRUG REACTIONS

In the past, there have been problems with timely reporting of ADRs by individual investigators to NCI and by NCI to FDA and to all investigators (e.g., MeCCNU). In part, this occurred as a result of misunderstanding of ADR reporting requirements for questionable, suspected, or confirmed drug reactions. .

Requirements for reporting of untoward findings are found in FDA regulations and on investigators' registration forms, as follows:

> NCI Responsibilities - Sponsors of INDs "shall promptly investigate and report to the Food and Drug Administration and to all investigators any findings associated with use of the drug that may suggest significant hazards, contraindication, side effects, and precautions pertinent to the safety of the drug. If the finding is alarming it shall be reported immediately and the clinical investigation discontinued until the finding is adequately evaluated and a decision reached that it is safe to proceed." [(21 CFR 312.1(a)(6)] form FD 1571, Notice of Claimed Investigational Exemption for a New Drug.

NCI as a sponsor has this responsibility.

> Investigator Responsibilities - "Any adverse effects that may reasonably be regarded as caused by, or probably caused by, the new drug shall be reported to the sponsor promptly, and if alarming, it shall be reported immediately." form FD 1573

NCI has recently revised its procedures for ADR reporting and evaluation, as depicted in Figure 4, Current NCI Procedures for Addressing Adverse Drug Reactions Reported to Them by Clinical Investigators in the Cancer Chemotherapy Program.

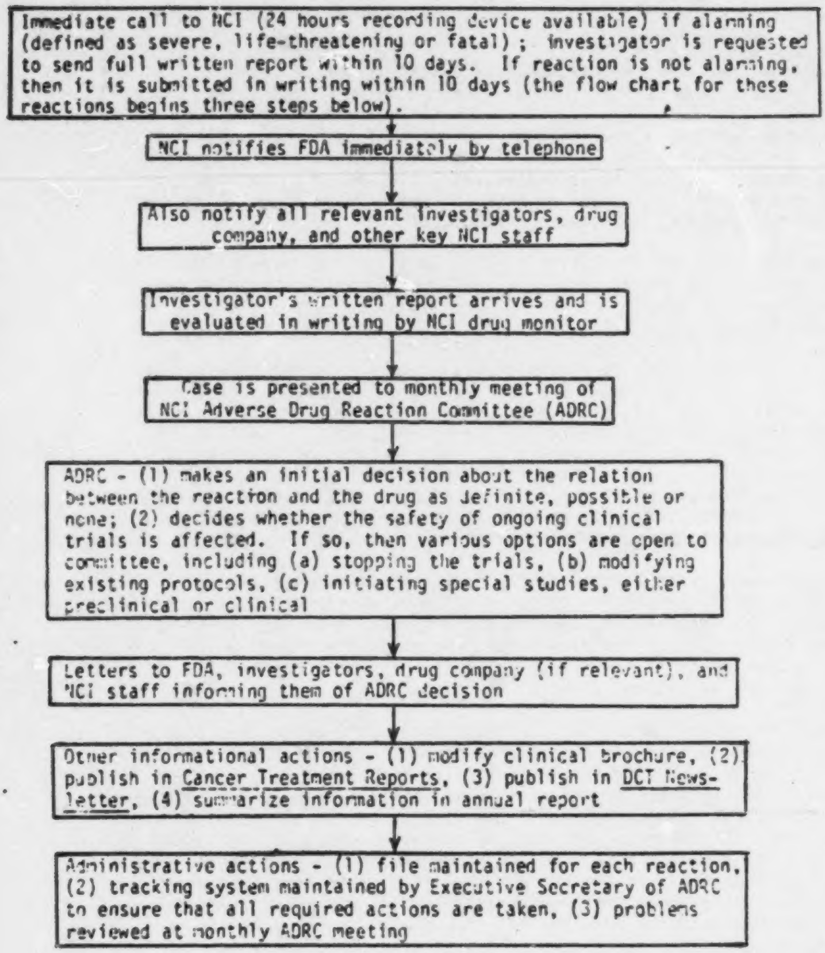
In addition, NCI has reminded its investigators of their responsibilities to report possible ADRs and of their obligations to report, immediately, any alarming reaction to an investigational new drug. While the clarified ADR reporting system has clearly defined responsibilities and actions of clinical investigators and NCI, scientific problems remain with regard to identifying accurately those reactions which are clearly associated with the drug. Since anticancer drugs may cause serious side effects, and since most patients receiving experimental drugs have been exposed to a series of other treatments and also have many serious medical events caused by the cancer, the problem of identifying ADRs with anticancer drugs is particularly difficult. Any ADR reporting system has to balance sensitivity with discrimination. If sensitivity is set extremely high, both NCI and FDA will be flooded with possible ADRs, and the job of identifying the true ADR will be virtually impossible. A real difficulty is with the state-of-the-art available to separate and quantify the ADR from the many other events and reactions that cancer patients on research protocols are experiencing.

The Task Force found that FDA and NCI modifications in ADR reporting stress the importance of timely reporting of ADRs and outline the subsequent steps that are taken with the determination of a possible or confirmed ADR. These steps may include alerting investigators, making changes in protocols and informed consent forms, putting a hold on the IND, and others.

The Task Force found that NCI's procedures and management practices are adequate to encourage reporting of findings from the investigator; to work-up the determination of a questionable, suspect, or confirmed ADR; and to respond to FDA requirements in a timely manner.

In addition, the Task Force found that FDA procedures and management practices are adequate to monitor the ADR work-up; to respond to reported ADRs; and within the state-of-the-art to ensure the protection of cancer patients from unsafe drugs by stopping the clinical trials.

ADVERSE DRUG REACTION REPORTING



Immediate call to NCI (24 hours recording device available) if alarming (defined as severe, life-threatening or fatal) ; investigator is requested to send full written report within 10 days. If reaction is not alarming, then it is submitted in writing within 10 days (the flow chart for these reactions begins three steps below).

NCI notifies FDA immediately by telephone

Also notify all relevant investigators, drug company, and other key NCI staff

Investigator's written report arrives and is evaluated in writing by NCI drug monitor

Case is presented to monthly meeting of NCI Adverse Drug Reaction Committee (ADRC)

ADRC - (1) makes an initial decision about the relation between the reaction and the drug as definite, possible or none; (2) decides whether the safety of ongoing clinical trials is affected. If so, then various options are open to committee, including (a) stopping the trials, (b) modifying existing protocols, (c) initiating special studies, either preclinical or clinical

Letters to FDA, investigators, drug company (if relevant), and NCI staff informing them of ADRC decision

Other informational actions - (1) modify clinical brochure, (2) publish in Cancer Treatment Reports, (3) publish in DCT Newsletter, (4) summarize information in annual report

Administrative actions - (1) file maintained for each reaction, (2) tracking system maintained by Executive Secretary of ADRC to ensure that all required actions are taken, (3) problems reviewed at monthly ADRC meeting

Figure 4. Current NCI Procedures for Addressing Adverse Drug Reactions Reported to Them by Clinical Investigators in the Cancer Chemotherapy Program

NCI
12/81

X. THERAPEUTIC INTENT

The Task Force heard widely disparate views on whether "therapeutic intent" exists in the initiation and conduct of Phase I clinical trials involving cytotoxic drugs. The Task Force understands this phrase to mean an intention, in some degree, to improve or to stabilize the condition of a specific patient to be inducted into a research protocol.

It is important that such an intent exists. Because the drugs used are so aversive, and because the patients are so dependent and vulnerable, it is more difficult to justify ethically Phase I cancer trials if there is no therapeutic intent.

There is no doubt that the medical community involved in the development of cancer drugs believes that there is a real and substantial therapeutic intent involved in the initiation and conduct of Phase I trials. Members of the medical community note that - (1) subjects are recruited into protocols only if they are terminally ill and conventional treatment has failed; (2) drugs are used only after animal testing has shown evidence of anticancer activity and review has deemed a drug to be promising; and, (3) [redacted]

On the other hand, critics point to the fact that preclinical animal testing is of little predictive value relative to particular human cancers, that response rate figures include minimal responses that should not be considered therapeutic in any real sense, and that, therefore, while there may be some small hope of benefit to patients, generally any benefit which occurs to a specific patient is mere "happenstance."

Two points confuse this discussion. First, there is a perception that a trial cannot be both therapeutic and experimental. The Task Force believes that perception is wrong. While in some cases an investigator may be interested solely in acquiring generalizable knowledge (as is the case when dealing with normal volunteers with other classes of drugs), when dealing with terminally ill patients and drugs which have shown some anticancer potential, it is possible to pursue both therapeutic and experimental goals. In fact, true singleness of purpose may be difficult to find even when physicians administer accepted drugs from their offices to patients to evaluate the impact of the drug not only for the effect on a particular patient but also for the usefulness of the drug on other patients.

The more difficult problem exists when a tension arises between the pursuit of experimental goals and the pursuit of therapeutic goals. For example, it may be that after initial doses of a certain cytotoxic drug, it becomes apparent that the toxicity in a patient is no longer acceptable, but that it is not clear that studies of the drug should be abandoned. Even in this case, conflict is avoidable. In such an event, the patient may be removed from the trial, but the trial may continue with additional patients. The second point of confusion is that Phase I trials are characterized by FDA procedures themselves as being for the purpose of establishing toxicity. [See for example, 21 CFR 312.1(a) form FD 1571]. For most Phase I trials, which involve solely normal volunteers, that characterization is correct. The case, however, is significantly different in Phase I cancer trials. Drugs are administered to sick patients to help them combat illness. To ignore that difference and merely point to a general characterization of Phase I trials is inappropriate.

On the basis of its deliberations, the Task Force has concluded that the real issue before it is not whether some measure of therapeutic intent exists in Phase I trials - clearly, for the reasons set out above, it is possible to establish such an intent. Rather, the concern is whether the low probability of response and the risk of toxic effects of the drug are made clear to the patient through the informed consent process.

We have heard considerable evidence that desperately ill patients are anxious to enter Phase I trials as a last resort. While the Task Force recognized that people do not have an absolute right to harm themselves consciously, neither should they be absolutely precluded from seeking treatment which holds out hope of benefit. If patient or family choice is to be the determinative factor, however, then ensuring that such a choice is a reasonably informed one is critical. A special problem in achieving informed consent in Phase I cancer trials is the physical condition of the patient and desperation of the patient and family. Thus, attention must be given not only to the information being conveyed, but also to whether the information is being "heard," or undue influence of physician on patient exists. Although there are extensive regulations governing the consent process as it relates to experiments involving human subjects, both NCI and FDA officials admitted that they have no means for ascertaining whether the actual interaction between the patient and the physician is conducted in an appropriate manner (see section on Protection of Human Subjects).

In summary, the Task Force found that therapeutic intent exists in Phase I trials. This conclusion acknowledges that - (1) the patients receiving the investigational drugs are terminally ill, and conventional treatment has failed; (2) these drugs are administered to patients only after animal testing has demonstrated evidence of anticancer activity and screening has shown a drug to be promising (although the validity of the screening process has not been proven); and, (3) since 1975, there has been an overall response rate of approximately 9.5 percent in the cancer patients receiving new anticancer drugs.

XI. PROTECTION OF HUMAN SUBJECTS

The physician investigator, IRBs, institutions, NCI, FDA, and the Office of Protection from Research Risks (OPRR), all have responsibilities to protect human subjects of research through the use, review, and monitoring of consent and investigative procedures.

The physician investigator and the IRB have primary responsibility for protecting human subjects through the development and review of sound research protocols and the informed consent form, and implementation of the informed consent process. It is also the physician's responsibility to modify consent forms to reflect current information on ADRs. The investigator utilizes the form in a process of interactions with the patient; it is ultimately the sensitivity, awareness, and skill of the physician which make possible an informed decision on the part of the patient. Informed consent is not a one time decision point, but rather an ongoing process which flows from the physician-patient relationship.

The IRB is the body designated by the funded institution to ensure the protection of human subjects through initial and continuing review of research proposals. [redacted] Part of this is directly related to the absence of specific direction and education of members. With the passage of virtually identical IRB and informed consent regulations by HHS and FDA (which has separate regulatory authority) in July of 1981, it is anticipated that this clarification of duties and responsibilities will enable the IRBs to play a more meaningful role.

The institution and OPRR share formal responsibility for protecting research subjects. The institution's responsibility is acknowledged through the submission of a general or special assurance.

FDA, with its mandate to protect the public from unsafe drugs, can request the sponsor (NCI) to include a toxicity warning in the consent form when FDA feels the benefit/risk ratio warrants that addition.

There are still concerns, however, about both the functioning of IRBs and the adequacy of informed consent for cancer patients in research protocols which must be pursued with vigilance by all the above parties to improve the process. Those studying the informed consent process in a variety of medical treatment and research situations have offered suggestions to minimize the possibility of coercion on the part of the physician and to enhance the decision-making capacity of the patient through a variety of special mechanisms. The Task Force believes that adherence to the HHS and FDA regulations will improve the informed consent process.

The cancer patient faces extremely difficult treatment decisions in traditional and research situations. It is crucial, therefore, that patient decisions be made on the basis of complete and frank information. In Phase I trials, for example, the physician disclosing information to the potential research participant must be particularly careful to describe fully "reasonably foreseeable risks and discomforts," "any benefits to the subject or others which may reasonably be expected," and to include a statement that "participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled." (45 CFR 46.116) The Task Force concurs that information disclosed for Phase I must include a statement about the small possibility of direct benefit to the patient him/herself.

[redacted]

In summary, while the physician and the IRB share primary responsibility for the adequacy of the consent process and the soundness of the research protocol, the institutions, NCI, OPRR, and FDA all have important roles in ensuring the protection of human subjects through compliance with and enforcement of HHS and FDA regulations.

Recommendations -

Additional steps should be taken to improve compliance with existing FDA and HHS regulations. They are as follows -

1. NCI and FDA reviewers of informed consent forms should become more familiar with the required elements of the FDA and HHS regulations and use a reference review guide that lists the required elements of the regulations to ensure that the consent forms are thorough and specific and are evaluated against the requirements.

2. Feedback from NCI and FDA review of informed consent forms should be made to IRBs and to investigators; FDA Bioresearch Monitoring inspections should categorize deficiences in informed consent forms from site visits so that summary data can be compiled for educational activities and to provide needed feedback.

3. IRBs should encourage lay members to review consent forms to determine that language is understandable and not unnecessarily technical, and encourage all members to use a review guide for review of informed consent forms.

4. OPRR should develop an educational program for all participants in the consent process - sponsors, institution representatives, and investigators - to spell out their respective responsibilities, and methods to ensure maximum communications of the risks and benefits of participation in clinical trials.

5. OPRR should - (a) proceed to select at random and review consent forms approved by IRBs; (b) expand the current review of grant summary statements for protection of human subjects to include NCI contracts; and (c) initiate reviews of investigators, IRBs, and institutions to determine adherence to regulations.

6. NCI should increase its operational ties with OPRR with regard to protection of the rights of cancer patients.

XII. COMPARISON OF FDA-NCI RELATIONSHIPS WITH FDA-INDUSTRY RELATIONSHIPS

Considerable concern has been expressed that in the area of cytotoxic drugs FDA is lax in its regulatory role toward NCI as compared with industry. Others see administrative and substantive program factors that warrant differences in FDA actions which do not constitute favoritism. The Task Force has considered several subject areas which have been identified by those who have spoken to the Task Force regarding those concerns, as follows:

A. Pre-1975 History -

Prior to 1975, FDA's regulatory stance toward NCI's cytotoxic program was lax, but since then has moved to a more vigorous position. History should no longer taint current understandings, which should derive from analyses of current activities.

B. Establishment of Mechanisms to Obtain Better Interaction Between FDA and NCI -

Establishment of improved communication channels between NCI and FDA (e.g., DMF, MOU, joint staff meetings) provides a closer relationship than between FDA and industry. These improvements are desirable and positive. Improved communication can increase understanding of cytotoxic drug development without compromising FDA's regulatory role. Full utilization of these communication channels has not yet been achieved, and is encouraged. Although there may be reasons for an arm's-length relationship between FDA and industry, there is no reason for such distance between FDA and NCI.

C. Administrative Letters to NCI Come From Higher FDA Levels than Do Those to Industry -

There is a policy for administrative letters to NCI on important regulatory matters to come from higher FDA levels than do those to industry.

> Recommendation - BD should define the appropriate level for sign-off responsibility for letters dealing with important regulatory matters and implement that decision consistently. The current inconsistency should be eliminated. Steps should be taken to ensure that Division-level personnel perform effectively and with reasonableness and sensitivity to all sponsors in accordance with BD policy.

D. Regulator to Regulatee Relationship of FDA and NCI -

Comments on reluctance of NCI to be regulated, or of FDA to regulate NCI should in no way cloud the clear and unequivocal position of all NCI and FDA policy level staff, i.e., that FDA must fulfill its regulatory responsibilities over NCI-sponsored cytotoxic drug INDs.

Energy should be directed toward resolving differences on the underlying substantive and procedural problems. Mutual education and understanding of the respective research and regulatory roles of NCI and FDA are important and would help both agencies perform their missions.

E. Does FDA Accept Lower Quality Work from NCI than from Industry?

Allegations that FDA accepts lower quality work from NCI than from industry have been considered in several areas.

1. Is FDA less demanding of NCI for toxicology data for cytotoxic drugs than for other drugs? Than it is of industry?

    The difference of the NCI and FDA approach to toxiciology of cytotoxic drugs compared with all other drugs are scientifically sound, are warranted in light of the cancer problem, and do not represent a compromise in quality. Further, there is no difference in the manner in which NCI or industry would be treated with regard to cytotoxic drug development since both can use the Toxiciology Protocol.

2. Does FDA accept lower quality experimental protocols from NCI than from industry?

    Clinical protocols for testing cytotoxic drugs in cancer patients are necessarily different from those used in many other drug trials because of difficulties in creating ethical, controlled clinical trials in a uniformly fatal disease and restrictions on numbers of patients to be studied with toxic drugs. Ideal scientific design must be compromised to achieve the best possible care to patients. As a result, many Phase II studies in the cytotoxic areas have employed historical controls and Phase II studies have employed combination therapies. Such differences have been, but should not be, construed to be of "lower quality." The NCI clinical protocol development and review process includes multiple layers of consideration by experienced program and investigator personnel that should ensure acceptable experimental and statistical design and generally sound submissions. As expected in any large effort, some instances of less than high quality work have been identified. NCI and FDA staff should analyze jointly the characteristics of those clinical protocols thought to be flawed for purposes of resolution of conflicting views and delineation of end points that would satisfy both agencies.

3. Does FDA accept from NCI submission of fewer needed data than from industry?

NCI submits fewer raw data to FDA than does industry; this is so because NCI does not take a drug through the NDA stage at which time raw data submissions are required. NDA submissions for cytotoxic drugs are made by pharmaceutical firms (which may use data obtained from NCI-supported studies). The current lack of FDA monitoring resulting from infrequency of NCI investigators doing NDA pivotal studies should not be attributed to the parallel but separate difference between industry and NCI as to the amount of raw data submitted.

4. Does FDA accept less chemical information and less evidence of agent purity from NCI than from industry?

Controversy regarding compromise of standards for chemical and purity information from NCI could not be assessed by this Task Force effort. NCI and FDA staff should analyze jointly the characteristics of those chemical and purity reports on cytotoxic drugs thought to be inadequate by FDA staff for purposes of resolution of conflicting views, and reaching agreement on standards to be used.

5. Does FDA accept less and tardy paperwork supporting INDs from NCI as compared with industry?

This allegation could not be assessed adequately by the Task Force. There were delinquency and tardiness of NCI reports prior to 1981. Since the beginning of 1981, the Investigational Drug Branch (IDB) record shows that annual reports have been submitted to FDA in a timely manner.

F. Does FDA Monitor NCI Less than It Monitors Industry?

The extent to which FDA monitors NCI INDs as compared with those from industry has been examined from several perspectives-

1. Preclinical Toxicity Testing

Preclinical toxicity testing requirement differences are due to differences between cytotoxic and other classes of drugs, and not to differences in FDA approaches to NCI and to industry.

2. Clinical Studies

"Monitoring" encompasses both "data verification" and "scientific program interim analysis." Current NCI data verification is significant and generally equal to that done by industry sponsors in Phase I and some Phase II studies, but NCI does none in Phase III studies. FDA does little direct data verification for cytotoxic drug studies of either NCI or industry. Because of FDA surveillance strategy, cytotoxic IND investigators have not been subjects of field inspections; this is true for both NCI and industry-sponsored studies.

3. Drug Distribution

A drug distribution system being implemented by NCI will meet monitoring needs of both NCI and FDA and likely will equal those of industry.

In summary, differences exist between FDA monitoring of NCI and industry, but they are not inappropriate. In some areas, improvements are needed. For cytotoxic drugs, no pervasive or significant policy of FDA favoring NCI by imposing less monitoring requirements than upon industry was found.

G. Unique Character of NCI's Group C Drugs

Establishment of Group C is not unique since industry has also used this mechanism for drug distribution. What is unique is the size of the NCI cytotoxic drug development program and its extension to a large but controlled subset of the health care delivery system. Group C drug status is reached by using standards different from those used for NDA approval and marketing. Group C drug status can be gained without submission of, or field inspection of, raw data; since this is integral to the NDA approval process, some FDA staff have less confidence in the reliability, or "quality," of the data used for approval. The highly controlled distribution through qualified physicians for use only on specified cancers confers on Group C status drugs a compensatory quality control.

Recommendation -

For purposes of resolving conflicting views within FDA and improving communication between NCI and FDA, a study should be performed regarding - (1) the characteristics of clinical protocols thought to be flawed by some FDA staff (which should result in methods to ensure higher quality of future protocols implemented by the NCI cytotoxic drug development program); (2) the characteristics of those chemical and purity reports on cytotoxic drugs thought inadequate by some FDA staff (which should result in agreement on the standards to be used in subsequent INDs); and (3) the allegations of some FDA staff of frequent and extensive absence of documents required for various parts of the investigational new drug program. The Task Force suggests that the responsibility for this effort be given to an organization other than NCI or BD.

XIII. COMMUNICATION PROBLEMS

Communication problems underlie a number of the difficulties with the NCI/FDA handling of the cytotoxic drug program. There is need for mutual respect for differences of opinion between the two agencies' staff and serious exploration of the important substantive problems about which differing views are held.

FDA. as a regulatory body, must assemble its single "agency view" on given issues so as to avoid confusing sponsors who must meet FDA requirements. It is critically important to reach an appropriate balance between intellectual freedom to express divergent ideas with the need for an organizational coherence of an agency's policies and positions. Divergent views cannot be allowed to impede the functioning of FDA.

The role of communication problems is discussed here in relation to issues covered in the previous section, Comparison of FDA-NCI Relationships with FDA-Industry Relationships.

A. Channels Established to Increase Communication Between FDA and NCI

New channels of communication between FDA and NCI established over the past few years are excellent in principle, but in practice have fallen short of expectations and potential. Improvements can result from distinguishing between scientific discussions and regulatory actions, and between formal and informal communications.

> Recommendation -
>
> NCI meetings should be structured for free exchange of ideas on the science and medicine of cytotoxic drugs while insulating those discussions from FDA regulatory functions of attending FDA staff. Relevant information from such meetings should be submitted formally from NCI to specific FDA IND files. Regulatory issues should be addressed formally in writing and responded to in writing. The FDA and NCI communication channels should be used fully.

B. Escalation of Administrative Letters to NCI to Higher FDA Levels

The Task Force has recommended that important administrative letters should be signed off at the same organizational level for all sponsors; NCI and industry should be treated alike. Whater its past rationale, the practice of escalation of review of administrative letters to NCI (but not to industry) to the Office of the BD Director has been associated with a failure of communication and/or understanding by some levels of FDA staff. Free and open discussions could have resolved the misunderstandings.

C. Regulator-Regulatee Relationships of FDA and NCI

Past comments have been interpreted as reflecting reluctance of NCI to be regulated and FDA to regulate NCI fully. There have been significantly different perspectives between NCI and FDA staff on intensity and purposes of monitoring, aggressiveness of regulatory action, views as to preclinical and clinical testing requirements, and other substantive issues. These should not cloud the fact that FDA and NCI policy level staff agree that FDA must fulfill its regulatory responsibilities over NCI as a sponsor of INDs.

D. FDA Acceptance of Lower Quality Work from NCI

Poor communication accounts for many of the strong disagreements about the quality of NCI work that FDA accepts. Important science and medicine issues are the bases for many disagreements. Examples are -

- Despite extensive study and review indicating that the new Toxicology Protocol is appropriate in the light of current knowledge, strong objections to it remain among some FDA staff. (As indicated in Section V, there is no single document that all agree is the new Toxiciology Protocol. This has resulted in considerable misunderstanding among FDA and NCI staff as to its details.);

- Including smaller number of patients and having fewer ideally controlled experiments in cancer drug trials is construed by some staff to be evidence of lower quality studies;

- Strong differences of opinion exist as to the extent of chemistry and purity information necessary before proceeding with the sequential phases of clinical trials.

Resolution of differing views on such important science and medicine issues is possible with analysis of new data and repeated examinations of the problems.

Poor communication has led to confusion between "raw data" and "fewer data" submissions by NCI. In turn, fewer raw data have been equated with poor quality submissions. This controversy has served as a proxy for an indirectly related problem -- that there is little monitoring of cytotoxic drug investigators. Concerns about excluding NCI-sponsored investigators from FDA field investigations should have been forthrightly addressed earlier.

> Recommendation - BD should reexamine its surveillance pattern for field inspection efforts and consider placing cytotoxic INDs higher on the priority list.

E. FDA Monitoring of NCI

"Monitoring" is a term used frequently without careful discrimination between the subsets of activities encompassed. Perceived differences in views about the degree of monitoring of NCI trials result in part from different uses of the term. Analysis of monitoring (both data verification and interim program analysis) of cytotoxic drug programs reveals no reduced FDA monitoring of NCI clinial trials as compared with those of industry. Differences of monitoring between cytotoxic drugs and other classes of drugs do occur.

F. Group C Drugs

Group C drugs provide a different path and use different criteria than the NDA to control and to distribute drugs widely to modify patterns of care for a given tumor type. The different criteria are believed by some FDA staff to be scientifically less rigorous and to allow inferior drugs to be widely distributed. Other FDA staff and the FDA Oncology Drugs Advisory Committee have endorsed the group C drug status concept. The important underlying issues need to be identified and analyzed, and new judgments made that will satisfy both high quality science and the best interests of cancer patients to whom cytotoxic drugs are given.

Summary

The critical substantive issues of cytotoxic drug development and procedural matters for resolution of program problems are of great importance to the health and welfare of the public. Communication problems contribute to some of the difficulties with the NCI/FDA handling of the cytotoxic drug program and warrant major efforts within and between the agencies to resolve differences. While retaining great tolerance for expression of differing veiws, movement must be made toward organizational coherence of agency policies necessary for the institutional performance of missions.

Differences of view among FDA BD staff on important issues underlying FDA's regulatory functions have been strong and long standing, have diverted important resources from performing these functions, and have clouded FDA's formal positions.

Bureau of Drugs Management

In addition to description of poor communications between and within FDA and NCI, the Task Force heard a number of individual allegations regarding personnel problems, low morale, and inefficient managerial practices of the FDA BD divisions and BD management dealing with cytotoxic drugs.

The Task Force lacked the time to assess the merit of many of these allegations. Even if proved in some instances, they may reflect problems that may realistically be difficult to solve.

> Recommendation -
>
> In view of the allegations, the Office of the Assistant Secretary of Health's Office of Management should undertake a management study of the BD divisions and BD managers dealing with cytotoxic drugs to examine areas about which questions have been raised, such as organization, personnel and staffing, budget, decision-making procedures, internal communications, morale, workload, filing system, and paperflow.

XIV. SANCTIONS

Judicious use of sanctions in appropriate cases serves several important purposes. Not only does it punish the wrongdoer, but it also - (1) provides a reminder to others of the requirements that were transgressed; (2) underscores the importance the agency places on these requirements; and (3) deters potential wrongdoers from acting improperly. The problems encountered with the NCI drug development program are not primarily the result of the existence or absence of sanctions, but there may be some unwillingness to use existing sanctions. Both NCI and FDA have significant steps each can take against wrongdoers if they so choose. NCI's main forms of leverage involve control over funding, control over participation in NCI-sponsored trials, and control over access to NCI-distributed drugs. NCI has, however, rarely imposed sanctions against violators of applicable rules and regulations.

FDA's major authority is denial or withdrawal of an IND.

The proper use of sanctions is appropriate and needed.

Recommendations -

1. **NCI should more actively impose sanctions against wrongdoers.**

2. NCI management officials should be reminded of their obligations to report violations of federal rules and regulations to appropriate law enforcement authorities, e.g., HHS Inspector General.

3. Sanctions should be considered against the institution as well as the individual wrongdoer when multiple violations occur at a single institution, when appropriate.

4. 45 CFR Part 74 should be amended to allow suspension or termination of a grant, not only for causes related to that grant, but for causes related to activities of the investigator in other contexts.

5. The Director, NIH, should review the NCI procedures for denying investigators use of NCI-sponsored drugs for clinical investigations to ensure that the procedures are fair and to provide for consistent treatment of investigators.

6. FDA and NIH should expedite development of plans and procedures for the sharing of information regarding ongoing and completed regulatory and monitoring investigations including the sharing of findings of wrongdoing with agencies and organizations (federal and nonfederal) outside HHS.

XV. SUMMARY

NCI's anticancer drug development program is a complex, unique scientific and therapeutic endeavor focussed on one facet of cancer research and treatment while FDA's BD has the role of regulating NCI's new drug development to ensure that unacceptably dangerous drugs are not used in the treatment of cancer in humans. These two agencies operate on the frontier of science and medicine to develop chemotherapy for more than 100 forms of cancer.

The Task Force assumed its charge with recognition of the pressure on NCI to succeed in the development of new drugs and the necessity that FDA ensure the timely approval of safe and effective new drugs. Against this background, and its deliberations, the Task Force concluded that --

1. The new Toxicology Protocol has been judged to be sound by a satisfactory process, but continuing review is needed;

2. A nationwide clinical testing program sponsored and supported by NCI has led to many chemotherapeutic agents now widely used in cancer. Approximately 40,000 patients annually survive because of these drugs. Some phases of the clinical trials need closer central management;

3. Recently augmented controls on the distribution of anticancer drugs by NCI to its investigators are sound and should minimize or eliminate the problem of drug leakage;

4. Within the limitations of the state-of-the-art, NCI and FDA procedures for addressing ADRs are acceptable for protecting the cancer patient from unnecessary risks;

5. Therapeutic intent exists in Phase I clinical trials involving new anticancer drugs;

6. Protection of the cancer patient through proper informed consent procedures can be improved by adherence to existing HHS and FDA regulations; the IRB and the physician share a major responsibility for the adequacy of the consent process and, in that role, may be helped by educational material provided to them by the sponsor (NCI), OPRR, and FDA;

7. The proper use of sanctions by both FDA and NIH is appropriate and needed against wrongdoing investigators and institutions;

8. The MOU is a useful document in which FDA and NCI may incorporate further managerial and operational understandings that may facilitate the activities in the development and regulation of anticancer drugs.

The Task Force found that recent NCI and FDA changes are positive and reflect efforts to improve management of the anticancer drug development program. The implementation of these changes and the recommendations of the Task Force will help to corract existing problems as the agencies continue to carry out effectively their respective roles. The Task Force believes that cancer patients have been aided and will in the future benefit from the anticancer drug development program.

APPENDIX A

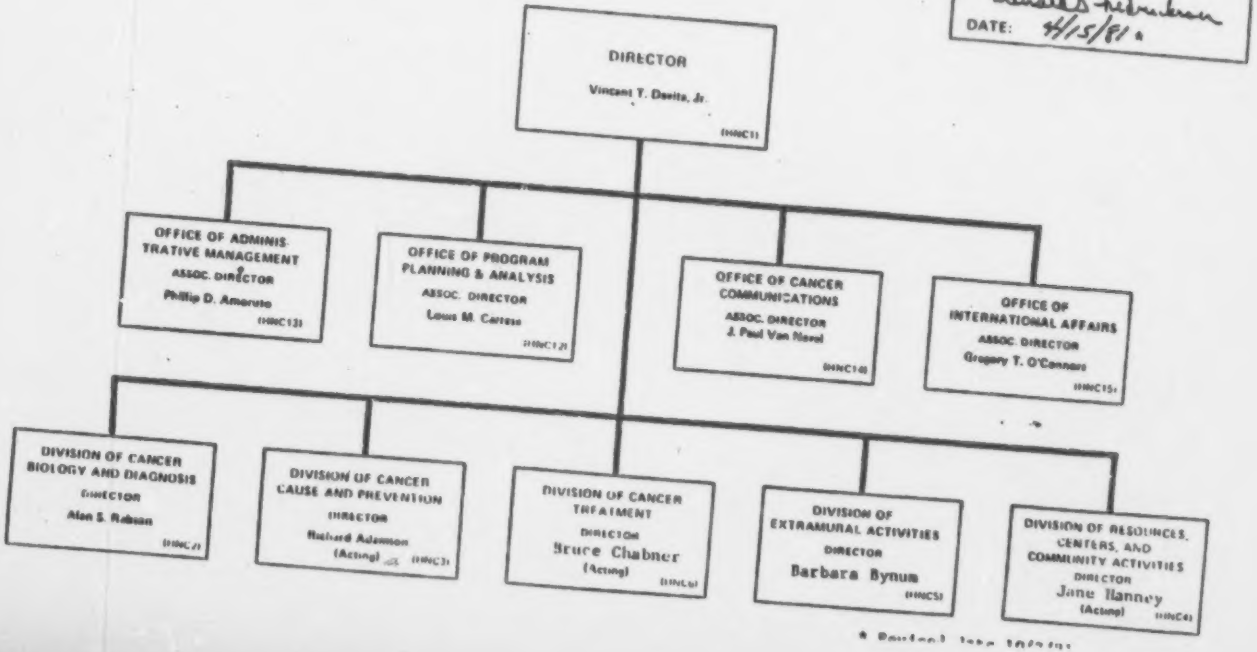
ORGANIZATIONAL CHARTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
National Institutes of Health

National Cancer Institute

APPROVED:
Donald S. Fredrickson
DATE: 4/15/81 *


DIRECTOR
Vincent T. DeVita, Jr.
(HNC1)
OFFICE OF ADMINISTRATIVE MANAGEMENT
ASSOC. DIRECTOR
Phillip D. Amoruso
(HNC13)
OFFICE OF PROGRAM PLANNING & ANALYSIS
ASSOC. DIRECTOR
Louis M. Carrese
(HNC12)
OFFICE OF CANCER COMMUNICATIONS
ASSOC. DIRECTOR
J. Paul Van Nevel
(HNC14)
OFFICE OF INTERNATIONAL AFFAIRS
ASSOC. DIRECTOR
Gregory T. O'Conner
(HNC15)
DIVISION OF CANCER BIOLOGY AND DIAGNOSIS
DIRECTOR
Alan S. Rabson
(HNC2)
DIVISION OF CANCER CAUSE AND PREVENTION
DIRECTOR
Richard Adamson
(Acting)
(HNC3)
DIVISION OF CANCER TREATMENT
DIRECTOR
Bruce Chabner
(Acting)
(HNC6)
DIVISION OF EXTRAMURAL ACTIVITIES
DIRECTOR
Barbara Bynum
(HNC5)
DIVISION OF RESOURCES, CENTERS, AND COMMUNITY ACTIVITIES
DIRECTOR
Jane Hanney
(Acting)
(HNC4)

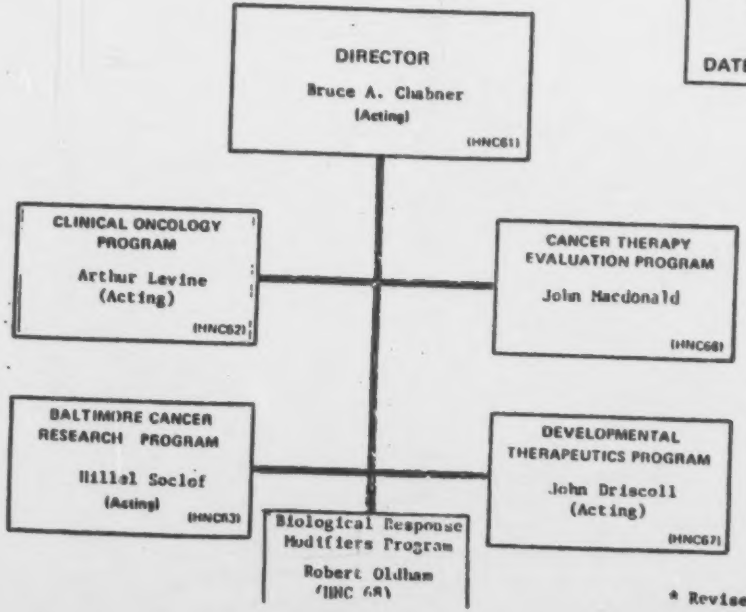
* Revised [illegible]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
National Institutes of Health

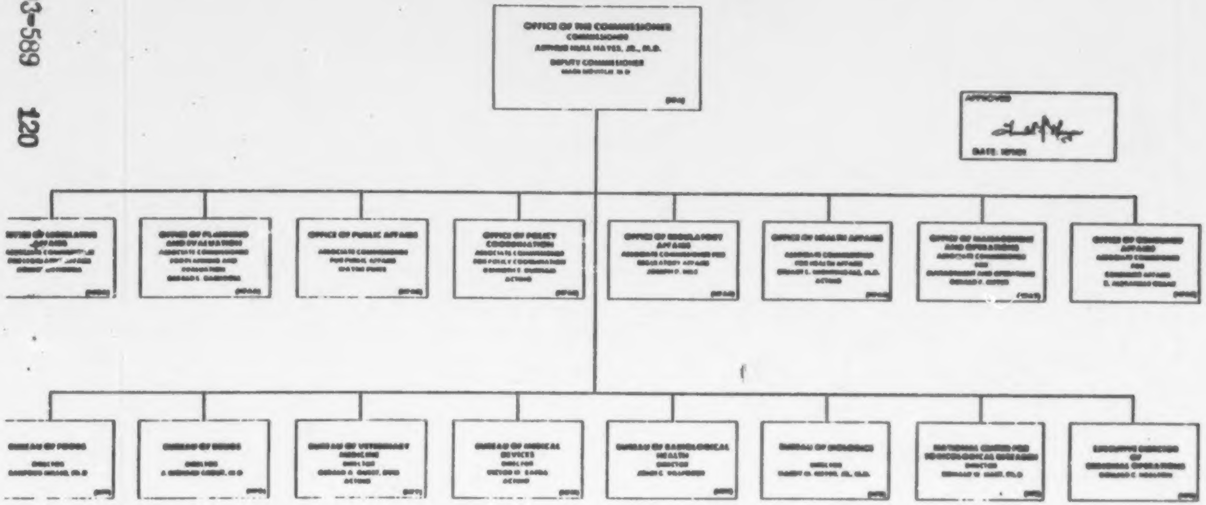
National Cancer Institute
Division of Cancer Treatment

APPROVED: DS Fredrickson
DATE: 4/15/81.


DIRECTOR
Bruce A. Chabner
(Acting)
(HNC61)
CLINICAL ONCOLOGY PROGRAM
Arthur Levine
(Acting)
(HNC62)
CANCER THERAPY EVALUATION PROGRAM
John Macdonald
(HNC68)
BALTIMORE CANCER RESEARCH PROGRAM
Hillel Soclof
(Acting)
(HNC63)
DEVELOPMENTAL THERAPEUTICS PROGRAM
John Driscoll
(Acting)
(HNC67)
Biological Response Modifiers Program
Robert Oldham
(HNC 68)

* Revised date 10/2/81

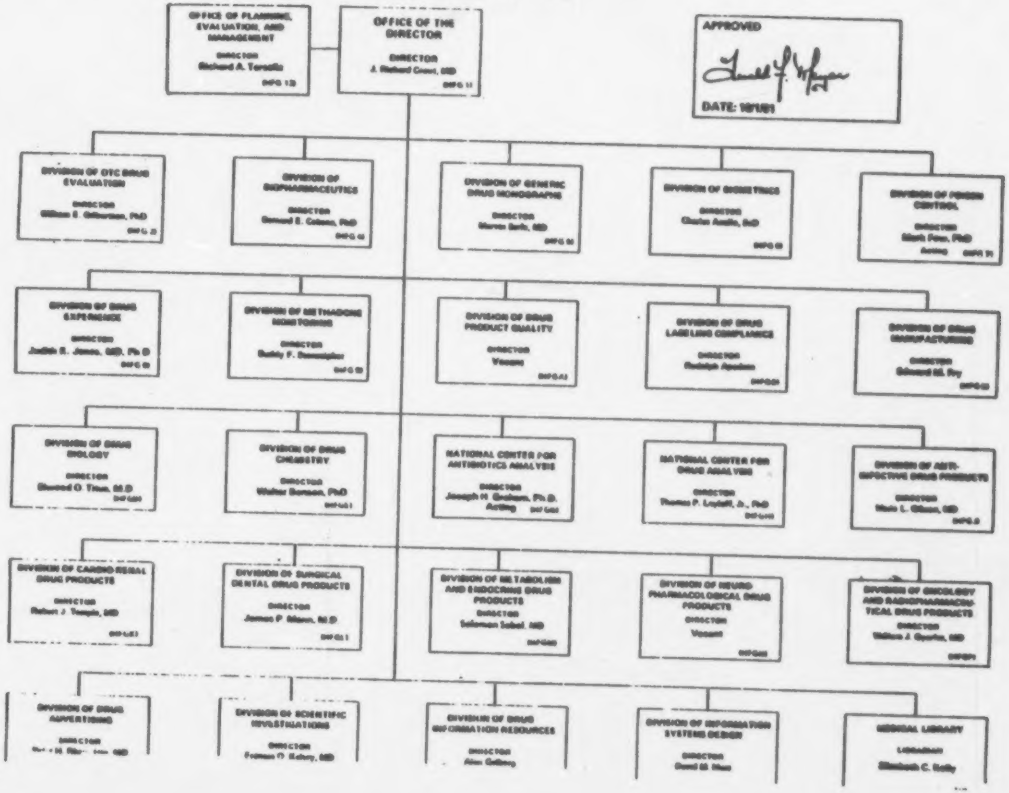
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION


OFFICE OF THE COMMISSIONER
COMMISSIONER
ARTHUR HULL HAYES, JR., M.D.
DEPUTY COMMISSIONER
APPROVED
DATE
OFFICE OF PUBLIC AFFAIRS
ASSOCIATE COMMISSIONER FOR PUBLIC AFFAIRS
OFFICE OF HEALTH AFFAIRS
ACTING
BUREAU OF FOODS
BUREAU OF DRUGS
BUREAU OF VETERINARY MEDICINE
BUREAU OF MEDICAL DEVICES
BUREAU OF RADIOLOGICAL HEALTH
BUREAU OF BIOLOGICS
NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH
DIRECTOR

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
Food and Drug Administration

BUREAU OF DRUGS


OFFICE OF PLANNING, EVALUATION, AND MANAGEMENT
DIRECTOR
Richard A. Teruzzi
OFFICE OF THE DIRECTOR
DIRECTOR
J. Richard Crout, MD
APPROVED
DATE: 10/1/81
DIVISION OF OTC DRUG EVALUATION
DIRECTOR
William E. Gilbertson, PhD
DIVISION OF BIOPHARMACEUTICS
DIRECTOR
Bernard E. Cabana, PhD
DIVISION OF GENERIC DRUG MONOGRAPHS
DIRECTOR
Marvin Seife, MD
DIVISION OF BIOMETRICS
DIRECTOR
Charles Anello, ScD
DIVISION OF POISON CONTROL
DIRECTOR
Acting
DIVISION OF DRUG EXPERIENCE
DIRECTOR
Judith K. Jones, MD, Ph.D
DIVISION OF METHADONE MONITORING
DIRECTOR
DIVISION OF DRUG PRODUCT QUALITY
DIRECTOR
Vacant
DIVISION OF DRUG LABELING COMPLIANCE
DIRECTOR
Rudolph Apodaca
DIVISION OF DRUG MANUFACTURING
DIRECTOR
Edward M. Fry
DIVISION OF DRUG BIOLOGY
DIRECTOR
Elwood O. Titus, M.D
DIVISION OF DRUG CHEMISTRY
DIRECTOR
Walter Benson, PhD
NATIONAL CENTER FOR ANTIBIOTICS ANALYSIS
DIRECTOR
Joseph H. Graham, Ph.D.
Acting
NATIONAL CENTER FOR DRUG ANALYSIS
DIRECTOR
Thomas P. Layloff, Jr., PhD
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
DIRECTOR
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
DIRECTOR
Robert J. Temple, MD
DIVISION OF SURGICAL DENTAL DRUG PRODUCTS
DIRECTOR
DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS
DIRECTOR
Solomon Sobel, MD
DIVISION OF NEURO PHARMACOLOGICAL DRUG PRODUCTS
DIRECTOR
Vacant
DIVISION OF ONCOLOGY AND RADIOPHARMACEUTICAL DRUG PRODUCTS
DIRECTOR
Vallace J. Gyarfas, MD
DIVISION OF DRUG ADVERTISING
DIRECTOR
DIVISION OF SCIENTIFIC INVESTIGATIONS
DIRECTOR
Frances O. Kelsey, MD
DIVISION OF DRUG INFORMATION RESOURCES
DIRECTOR
Alan Gelberg
DIVISION OF INFORMATION SYSTEMS DESIGN
DIRECTOR
MEDICAL LIBRARY
LIBRARIAN
Elizabeth C. Kelly

APPENDIX B

PERSONNEL INTERVIEWED BY THE TASK FORCE

NATIONAL CANCER INSTITUTE PERSONNEL
INTERVIEWED BY THE NATIONAL CANCER INSTITUTE - FOOD AND DRUG ADMINISTRATION TASK FORCE ON INVESTIGATION NEW DRUGS

Chabner, Dr. Bruce A.
  Acting Director, Division of Cancer Treatment

DeVita, Dr. Vincent T., Jr.
  Director, National Cancer Institute

DeWys, Dr. William
  Acting Chief, Clinical Investigations Branch
  Division of Cancer Treatment

Driscoll, Dr. John
  Acting Director for Developmental Therapeutics
  Developmental Therapeutics Program
  Division of Cancer Treatment

Henney, Dr. Jane
  Special Assistant for Clinical Affairs
  Division of Cancer Treatment

Hoth, Dr. Daniel B.
  Chief, Investigational Drug Branch
  Cancer Therapy Evaluation Program
  Division of Cancer Treatment

Kisner, Dr. Daniel L.
  Deputy Associate Director, Cancer Therapy Evaluation Program
  Division of Cancer Treatment

Lowe, Dr. Michael C.
  Acting Chief, Toxicology Branch
  Developmental Therapeutics Program
  Division of Cancer Treatment

Macdonald, Dr. John S.
  Associate Director, Cancer Therapy Evaluation Program
  Division of Cancer Treatment

Mackie, Ms. Elise
  Program Analyst, Cancer Therapy Evaluation Program
  Division of Cancer Treatment

Marsoni, Dr. Silvia
  Chief, Drug Evaluation and Reporting Section
  Investigational Drug Branch
  Cancer Therapy Evaluation Program
  Division of Cancer Treatment

NCI Personnel Interviewed

Schepartz, Dr. Saul A.
Deputy Director, Division of Cancer Treatment

Vilk, Mr. Paul J.
Pharmacist, Cancer Therapy Evaluation Program
Division Of Cancer Treatment

FOOD AND DRUG ADMINISTRATION PERSONNEL
INTERVIEWED BY THE NATIONAL CANCER INSTITUTE - FOOD AND DRUG ADMINISTRATION
TASK FORCE ON INVESTIGATIONAL NEW DRUGS

Brisson, Mr. Ernest L.
  Director, Bioresearch Monitoring Staff
  Office of Regulatory Affairs

Crout, Dr. J. Richard
  Director, Bureau of Drugs

Finkel, Dr. Marion J.
  Associate Director for New Drug Evalution
  Bureau of Drugs

Guarino, Dr. Anthony M.
  Pharmocologist, Division of Oncology and Radiopharmaceutical Drug Products
  Bureau of Drugs

Gyarfas, Dr. William J.
  Director, Division of Oncology and Radiopharmaceutical Drug Products
  Bureau of Drugs

Hamric, Ms. Kay
  Staff Assistant to the Commissioner, Food and Drugs

Hayes, Dr. Arthur Hull, Jr.
  Commissioner, Food and Drugs

Hensley, Dr. Michael J.
  Medical Officer, Clinical Investigations Branch
  Division of Scientific Investigations
  Bureau of Drugs

Johnson, Dr. John R.
  Medical Officer, Oncology Section, Division of Oncology and
  Radiopharmaceutical Drug Products
  Bureau of Drugs

Kelsey, Dr. Frances O.
  Director, Division of Scientific Investigations
  Bureau of Drugs

Lisook, Dr. Alan B.
  Chief, Clinical Investigations Branch
  Division of Scientific Investigations
  Bureau of Drugs

Nightingale, Dr. Stuart
  Acting Associate Commissioner for Health Affairs

Ottes, Mr. Ronald T.
  Deputy Executive Director of Regional Operations

FDA Personnel

Richman, Dr. David J.
Supervisory Pharmacologist, Division of Oncology and Radiopharmaceutical Drug Products
Bureau of Drugs

Ripper, Ms. Leah W.
Consumer Safety Officer, Division of Oncology and Radiopharmaceutical Drug Products
Bureau of Drugs

Turner, Dr. Gurston D.
Pharmacologist, Division of Scientific Investigations
Bureau of Drugs

Walker, Dr. Howard L.
Supervisory Medical Officer, Oncology Section
Division of Oncology and Radiopharmaceutical Drug Products
Bureau of Drugs

Wilms, Mr. Heinz G.
Deputy Director, Division of Scientific Investigations
Bureau of Drugs

Wood, Ms. Rebecca
Supervisor of Chemistry Reviews
Division of Oncology and Radiopharmaceutical Drug Products
Bureau of Drugs

Young, Dr. Robert S.K.
Medical Officer, Oncology Section
Division of Oncology and Radiopharmaceutical Drug Products
Bureau of Drugs

OTHER PERSONS
INTERVIEWED BY THE NATIONAL CANCER INSTITUTE - FOOD AND DRUG ADMINISTRATIO
TASK FOR ON INVESTIGATIONAL NEW DRUGS

Bernard, Ms. Sharon
  Human Resources Division
  U.S. General Accounting Office

Brandt, Dr. Edward N., Jr.
  Assistant Secretary for Health
  Department of Health and Human Services
  Public Health Service

Capron, Mr. Alexander Morgan
  Executive Director, President's Commission for the Study of Ethical Problems in Medicince and Biomedical and Behavioral Research

Fenstermaker, Mr. Carl
  Group Director
  Human Resources Division
  U.S. General Accounting Office

Horton, Ms. Linda
  Deputy Chief Counsel for Regulations and Hearings
  Office of the General Counsel
  Deparment of Health and Human Services
  Public Health Service

McCarthy, Dr. Charles R.
  Director, Office for Protection from Research Risks
  Office of the Director
  National Institutes of Health

MacKay, Dr. Charles R.
  Deputy Director, Office for Protection from Research Risks
  Office of the Director
  National Institutes of Health

Michie, Mr. James F.
  Chief Investigator, Subcommittee on Investigations and General Oversight of the Committee on Labor and Human Resources, United States Senate

Mishkin, Ms. Barbara
  Deputy Director, President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research

Parker, Ms. Terri Kay
  Subcommittee on Investigations and General Oversight of the Committee on Labor and Human Resources, United States Senate

Other Persons Interviewed

Raub, Dr. William F.
Associate Director for Extramural Research and Training
Office of the Director
National Institutes of Health

Royds, Dr. Robert B.
Vice President, G. H. Besselaar Associates
Princeton, New Jersey
Contractor to NCI to Clinical Trials Monitoring Service

Smith, Dr. Craig G.
Director, Systems Consulting
Mathtech, A Division of Mathematics, Inc.
Princeton, New Jersey
Contractor to NCI to Clinical Trials Monitoring Service

APPENDIX C

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
October 5, 1981	Meeting of Task Force Members Only		
October 9, 1981	Dr. J. Richard Crout, Director, Bureau of Drugs, FDA	X	
	Dr. Marion J. Finkel, Associate Director for New Drug Evaluation, Bureau of Drugs, FDA	X	
	Dr. Bruce A. Chabner, Acting Director, Division of Cancer Treatment, NIH	X	
	Dr. Jane Henney, Acting Deputy Director, National Cancer Institute, NIH	X	
October 14, 1981	Meeting of Task Force Members Only		
October 19, 1981	Meeting of Task Force Members Only		
October 20, 1981	Dr. Jane Henney		X
October 22, 1981	Dr. John S. Driscoll, Acting Associate Director for Developmental Therapeutics, Division of Cancer Treatment, NCI, NIH (also Head, Drug Design Chemistry Section, Laboratory of Medicinal Chemistry and Biology, Developmental Therapeutics Program, DCT, NCI, NIH)	X	
	Dr. Michael C. Lowe, Acting Chief, Toxicology Branch, Developmental Therapeutics Program, DCT, NCI, NIH	X	

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
October 22, 1981 (Continued)	Dr. John S. Macdonald, Associate Director, Cancer Therapy Evaluation Program, DCT, NCI, NIH	X	
	Dr. Daniel B. Hoth, Chief, Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment, NCI, NIH	X	
October 26, 1981	Dr. Daniel B. Hoth	X	
	Dr. John S. Macdonald	X	
	Ms. Kay Hamric, Staff Assistant to the Commissioner, FDA		X
October 27, 1981	Mr. William Dommel, Assistant Director, Office for Protection from Research Risks, OD, NIH		X
	Dr. Charles R. McCarthy, Director, Office for Protection from Research Risks, OD, NIH		X
	Dr. Charles R. McKay, Deputy Director, Office for Protection from Research Risks, OD, NIH		X
October 28, 1981	Dr. Charles R. McCarthy		X
	Dr. Charles R. McKay		X
October 29, 1981	Dr. Daniel B. Hoth		X
	Dr. Robert S.K. Young, Medical Officer, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, FDA	X	

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
November 4, 1981	Dr. William J. Gyarfas, Director, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, FDA	X	
	Dr. Michael J. Hensley, Medical Officer, Division of Scientific Investigations, Bureau of Drugs, FDA	X	
November 5, 1981	Dr. Craig G. Smith, Director, Systems Consulting, Mathtech, A Division of Mathematica, Inc., Contractor to NCI to Clinical Trials Monitoring Service	X	
	Dr. Robert B. Royds, Vice President, G.H. Besselaar Associates, Contractor to NCI to Clinical Trials Monitoring Service	X	
	Dr. Daniel B. Hoth	X	
	Dr. Anthony M. Guarino, Pharmacologist, Division of Oncology and Pharmaceutical Drug Products, Bureau of Drugs, FDA	X	
	Mr. Ernest L. Brisson, Director, Bioresearch Monitoring Staff, Office of Regulatory Affairs, FDA	X	
November 9, 1981	Mr. Heinz G. Wilms, Deputy Director, Division of Scientific Investigations, Bureau of Drugs, FDA	X	

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
November 9, 1981 (Continued)	Dr. Frances O. Kelsey, Director, Division of Scientific Investigations, Bureau of Drugs, FDA	X	
	Dr. Marion J. Finkel, Associate Director for New Drug Evaluation, Bureau of Drugs, FDA	X	
	Dr. Charles R. McCarthy	X	
November 12, 1981	Mr. Alexander Morgan Capron, Executive Director and	X	
	Ms. Barbara Mishkin, Deputy Director President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research	X	
	Dr. Howard L. Walker, Supervisory Medical Officer, Oncology Section, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, FDA	X	
	Ms. Laurie Meade, Field Inspector, FDA	X	
	Mr. Ronald T. Ottes, Deputy Executive Director, Regional Operations, FDA	X	
	Dr. Michael J. Hensley	X	
November 13, 1981	Dr. Jane Henney		X
November 16, 1981	Dr. Daniel B. Hoth		X

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
November 19, 1981	Ms. Leah W. Ripper, Consumer Safety Officer Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, FDA	X	
	Dr. John R. Johnson, Medical Officer, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, FDA	X	
	Dr. Rebecca H. Wood, Supervisor of Chemistry Reviews, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs	X	
	Dr. Stuart L. Nightingale, Acting Associate Commissioner for Health Affairs, FDA	X	
November 20, 1981	Mr. Carl Fenstermaker, Group Director, Human Resources Division, U.S. General Accounting Office (GAO)		X
	Ms. Sharon Bernard, Human Resources Division, U.S. GAO		X
November 23, 1981	Dr. Edward N. Brandt, Jr., Assistant Secretary for Health	X	
	Dr. William F. Raub, Associate Director for Extramural Research and Training, NIH	X	
	Dr. Alan B. Lisook, Chief, Clinical Investigations Branch, Division of Scientific Investigations, Bureau of Drugs, FDA	X	

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
November 24, 1981	Dr. Frances O. Kelsey		X
	Mr. Heinz G. Wilms		X
	Dr. John S. Macdonald		X
	Dr. Saul A. Schepartz, Deputy Director Division of Cancer Treatment, NCI, NIH		X
	Dr. Richard Simon, Chief, Biometric Research Branch, Division of Cancer Treatment, NCI, NIH		X
November 25, 1981	Meeting of Task Force Members Only		
November 30, 1981	Meeting of Task Force Members Only		
December 1, 1981	Dr. John S. Macdonald	X	
	Dr. Daniel B. Hoth	X	
	Dr. Gurston D. Turner, Division of Scientific Investigations, Bureau of Drugs, FDA	X	
	Dr. Daniel L. Kisner, Deputy Associate Director, Cancer Therapy Evaluation Program, DCT, NCI, NIH	X	
	Dr. William DeWys, Acting Chief, Clinical Investigations Branch, DCT, NCI, NIH	X	

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
December 3, 1981	Mr. James F. Michie, Chief Investigator and	X	
	Ms. Terri Kay Parker, Staff Counsel, Subcommittee on Investigations and General Oversight, Committee on Labor and Human Resources, U.S. Senate	X	
December 11, 1981	Dr. J. Richard Crout	X	
December 14, 1981	Meeting of Task Force Members Only		
December 16, 1981	Dr. Vincent T. DeVita, Jr., Director, NCI	X	
December 17, 1981	Dr. Arthur Hull Hayes, Jr., Commissioner, Food and Drugs	X	
December 21, 1981	Meeting of Task Force Members Only		
December 23, 1981	Meeting of Task Force Members Only		
January 4, 1982	Meeting of Task Force Members Only		
January 7, 1982	Meeting of Task Force Members Only		

VOLUME II

REPORT

on

ANTICANCER DRUGS: THE NATIONAL CANCER INSTITUTE'S DEVELOPMENT AND THE FOOD AND DRUG ADMINISTRATION'S REGULATION

by

Task Force on NCI-FDA
Investigational New Drugs

January 28, 1982

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

VOLUME II REPORT
on
ANTICANCER DRUGS:
THE NATIONAL CANCER INSTITUTE'S DEVELOPMENT AND THE FOOD AND DRUG ADMINISTRATION'S REGULATION

Report of the

Task Force on National Cancer Institute-
Food and Drug Administration Investigational New Drugs

January 28, 1982

Lowell T. Harmison, Ph.D.,
Chairman, Task Force
Science Advisor, Office of the
Assistant Secretary of Health,
U.S. Public Health Service

Lionel Bernstein, M.D., Ph.D.,
Vice-Chairman,
Former Director, Lister Hill
National Center for Biomedical
Communications, NLM, NIH

John Duffy, M.D.,
Deputy Associate Commissioner for Health Affairs
(Professional Relations), FDA

John R. Farrell, M.D., Operations
Management Staff, Office of
Management, OASH

David W. Fraser, M.D., Assistant
Director for Medical Science,
Bacterial Diseases Division,
Center for Infectious Diseases,
CDC

Paul J. Gilligan, M.H.S., Senior
Management Analyst, Office of
Management, OASH

Robert S. Gordon, Jr., M.D., M.H.S.
Special Assistant to the
Director, NIH

Jerome Levine, M.D., Chief,
Pharmacologic and Somatic
Treatments Research Branch,
Division of Extramural
Research Programs, NIMH,
ADAMHA

Joel M. Mangel, J.D., Deputy
Assistant General Counsel,
Public Health Division, Office
of the General Counsel, Office
of the Secretary, HHS

Lawrence R. Rose, M.D., Associate Director for Professional
Services, National Center for
Health Services Research, OHRST

Joan P. Porter, M.Sc.,
Executive Secretary,
Special Assistant to the
Director, Division of
Research Grants, NIH

Also working closely with the Task Force: Jack Blaine, M.D., Pharmacologic and Somatic Treatments Research Branch, Division of Extramural Research Programs, NIMH, ADAMHA; Richard J. Riseberg, J.D., Chief, National Institutes of Health Branch, Office of the General Counsel, Office of the Secretary, HHS; Anita Eichler, M.A., Division of Mental Health Service Programs, NIMH, ADAMHA, and Irene Shifren, Ph.D., formerly of ADAMHA.

Carol Peterson, Management Analyst, Office of Management Support, NIMH, ADAMHA; Judy Fouche, Editorial Assistant, Division of Personnel Management, NIH; Rebecca A. Dick, OASH; and Ellen Byrd, Division of Research Grants, NIH, also assisted the Task Force.

Table Of Contents

Page

Preface i

List of Figures and Tables iii

Abbreviations v

I. Introduction. 1

II. Cytotoxic Drugs - Background. 4

III. A Review of Two Cases Concerning NCI's Anticancer Drug Program Specific IND Cases. 12

IV. Memorandum of Understanding 15

V. Toxicology Protocol 19

VI. Clinical Trials 31

VII. Investigational New Drug Distribution and Investigators 50

VIII. NCI Investigator-Sponsor Roles: An Alternative 59

IX. Adverse Drug Reactions. 65

X. Therapeutic Intent. 68

XI. Protection of Human Subjects. 70

XII. Comparison of FDA-NCI Relationships with FDA - Industry Relationships. 82

XIII. Communication Problems 103

XIV. Sanctions. 110

XV. Summary. 119

Appendices in Volume I and Volume II

Appendix A - Organizational Charts

Appendix B - Personnel Interviewed by the Task Force

Appendix C - Chronological List of Task Force Meetings

Appendices in Volume II Only

Appendix D - List of Additional Meetings of the Task Force

Appendix E - List of Some Source Materials Available to the Task Force

Appendix F - Memorandum of Understanding Relative to Anticancer Drug Development

Appendix G - Memorandum dated December 1, 1981, to Dr. Lowell Harmison, Chairman, Task Force on NCI-FDA Investigational New Drugs from Associate Director for Extramural Research and Training, OD, NIH, subject: "Follow-up to November 23 Meeting" (regarding NIH Alert System).

Preface

To provide the findings of the Task Force within a 3 month period. as requested by the Assistant Secretary for Health, DHHS, a decision was made to present the general findings and recommendations in a summary volume (Volume I) and subsequently, more detailed background and supporting material in a followup document (Volume II).

Volume I was completed and submitted to the Assistant Secretary for Health on January 8, 1982. This approach was feasible because Task Force members had prepared papers on topics relating to the Task Force's mission. The Task Force discussed these papers as a lengthy working draft that led to the recommendations in Volume I. The Task Force then attempted to reflect the consensus reached in Volume I by making appropriate changes in the larger Volume II. While the recommendations in the two volumes are the same, there may be minor discrepancies in the texts.

The following sections are identical in Volumes I and II: (1) Section I, Introduction; (2) Section III, A Review of Two Cases Concerning NCI's Anticancer Drug Program, Specific IND Cases; (3) Section X, Therapeutic Intent; and (4) Section XV, Summary.

Figures and Tables

Section

Figure 1 - National Cancer Institute Drug Development Program. II

Figure 2 - Current Cytotoxic Drug Distribution and Cancer Treatment Plan II

Figure 3 - Planned 1986 Cytotoxic Drug Distribution and Cancer Treatment Plan II

Figure 4 - Monitoring of NCI Clinical Investigations of Cytotoxic Drugs . VI

Figure 5 - Characteristics of Investigational New Drug Distribution . . VII

Figure 6 - Current NCI Procedures for Addressing Adverse Drug Reactions Reported to Them by Clinical Investigators in the Cancer Chemotherapy Program IX

Figure 7 - Historical Review of Events Relating to Protection of Human Subjects in Research/Informed Consent. XI

Figure 8 - The NCI Process of Review for Protocols and Informed Consent Forms for Phase I. XI

Figure 9 - The NCI Process of Review for Protocols and Informed Consent Forms for Phases II and III. X

Table 1 - Organ-Specific Toxicity of 25 Toxic Drugs in Humans: Comparison of Observed Predictiveness of Dog Toxicity Results with That Expected by Chance Alone. V

Table 2 - Clinical Cooperative Groups VII

Table 3 - Clinical and Comprehensive Cancer Centers and New Drug Studies Groups. VII

Exhibit - Form NIH 986, National Institutes of Health, National Cancer Institute, Clinical Drug Request. VII

ABBREVIATIONS

A

ADAMHA - Alcohol, Drug Abuse and Mental Health Administration
ADR - Adverse Drug Reaction
ADRC - Adverse Drug Reaction Committee

B

BD - Bureau of Drugs (FDA)
BIMO - Bioresearch Monitoring Program
BSC - Board of Scientific Counselors (DCT/NCI)

C

CCOP - Community Clinical Oncology Program
CDC - Centers for Disease Control
CFR - Code of Federal Regulations
CIB - Clinical Investigations Branch (CTEP/DCT/NCI)
CTEP - Cancer Therapy Evaluation Program
CTEP-IS - Cancer Therapy Evaluation Program Information Service
CTMS - Clinical Trials Monitoring Service

D

DCT - Division of Cancer Treatment
DMF - Drug Master File
DN - Decision Network
DNC - Decision Network Committee
DOD - Department of Defense
DSI - Division of Scientific Investigations (BD/FDA)
DTP - Developmental Therapeutics Program (DCT/NCI)

E

ECOG - Eastern Cooperative Oncology Group

F

FDA - Food and Drug Administration
FD 1571 - Notice of Claimed Investigational Exemption for a New Drug
FD 1573 - Statement of Investigator Form
FD 1639a - Drug Experience Report, Short Form
FY - Fiscal Year

H

HMTD - Human Maximum Tolerated Dose
HHS - Department of Health and Human Services
HHS 596 - Protection of Human Subjects Certification Form

I

IDB - Investigational Drug Branch (CTEP/DCT/NCI)
IND - Investigational New Drug Application
IRB - Institutional Review Board

L

LD - Lethal Dose

M

MeCCNU (Methyl CCNU) - 1-(2-Chlorethyl)-3-(4-methylcyclohexyl)-1-nitrosourea
MEDLARS - Medical Literature Analysis and Retrieval System (of NLM)
MOU - Memorandum of Understanding
5-MTHHF - 5-Methyltetrahydrohomofolate

N

NCAB - National Cancer Advisory Board
NCI - National Cancer Institute (NIH)
NDA - New Drug Application
NIH - National Institutes of Health
NIH 986 - Clinical Drug Request Form
NIMH - National Institute of Mental Health
NLM - National Library of Medicine

O

OASH - Office of the Assistant Secretary for Health
OHRST - Office of Health Research Statistics and Technology
OPRR - Office of Protection from Research Risks (of NIH)

P

PHS - Public Health Service
PI - Principal Investigator
PRB - Pharmaceutical Resources Branch (CTEP/DCT/NCI)

S

SWOG - Southwest Oncology Group

T

TDL - Toxic Dose Low

REPORT ON ANTICANCER DRUGS:
THE NATIONAL CANCER INSTITUTE'S DEVELOPMENT AND THE FOOD AND DRUG ADMINISTRATION'S REGULATION

I. INTRODUCTION

On October 2, 1981, Dr. Edward N. Brandt, Jr., Assistant Secretary for Health, Department of Health and Human Services, established a Task Force on investigational new drugs to assess the National Cancer Institute's (NCI) anticancer drug development program and the Food and Drug Administration's (FDA) regulation of these anticancer drugs.

The Task Force was formed at a time when much Congressional and public media attention had been drawn to NCI's cytotoxic drug development program and the investigational new drug process. A series of Congressional hearings that highlighted issues included-

> On April 1, 1981, Representative Albert Gore, Jr., Chairman of the Subcommittee on Investigations and Oversight of the United States House of Representatives' Committee on Science and Technology, held hearings concerning ethical and institutional problems in biomedical research.
>
> On May 21, 1981, Senator Paula Hawkins chaired a hearing of the Subcommittee on Investigations and General Oversight of the United States Senate's Labor and Human Resources Committee on oversight of the National Cancer Program and the last 10 years of progress toward a cure for cancer.
>
> On June 2, 1981, the full Senate Labor and Human Resources Committee, chaired by Senator Orrin Hatch, met concerning NCI contracting procedures.
>
> In late October and early November 1981, hearings were held in the House and in the Senate regarding the investigational new drug process and related issues. Particular areas of concern were protection of human subjects, public accountability for the testing of specific drugs such as MeCCNU, adverse drug reaction (ADR) reporting, and the relationship between NCI and FDA.

The charges in the press and testimony at the hearings highlighted a number of issues concerning NCI and FDA. The alleged problems were to be looked at against a background of new management of NCI and numerous important changes instituted over the past few years.

Task Force Effort - Scope and Limitations

Dr. Brandt charged the Task Force "(1) to assess NCI management systems for monitoring INDs [Investigational New Drug application]; (2) to assess FDA's review of NCI activities relative to these drugs; and (3) to develop recommendations for improvement that may stem from the findings of the Task Force."

The Task Force structured its study to examine the investigational new drug process for cytotoxic drugs from drug identification through toxicological and clinical evaluation of a drug to the point of availability to the cancer patient. Therapeutic intent, informed consent, ADRs, monitoring, accountability, and drug control are areas of concern as a new drug moves through the several stages of its development and evaluation. These critical areas of concern were examined in relationship to the several steps in the drug development and evaluation process.

The Task Force efforts were directed, for the most part, to cytotoxic drugs, although, for several issues, the problems were generic in nature, and cytotoxic drugs reflected broader drug development and testing problems.

The focus of the work was on the Division of Cancer Treatment (DCT) in NCI and the Bureau of Drugs (BD) in FDA, although others in NCI, National Institutes of Health (NIH), and FDA were consulted. Organizational charts for FDA and NCI are found in Appendix A. The Task Force members believed that views of investigators, institutional review board (IRB) members, and industry representatives would have been valuable if there had been additional time.

Ninety days was a short interval in which to address the numerous issues that were associated with the Task Force mission. An exhaustive investigation of all data presented to resolve discrepancies or to explore implications and perceptions given by interviewees was not possible. Because of the many facets of the cytotoxic drug program to be examined, the Task Force was composed of members from many different fields and disciplines; the advantage of diversity of views thereby gained necessarily balanced against the limited depth of expertise in the individual substantive areas considered. A deliberate decision was made to exclude persons who have ever had assignments in the cytotoxic drug development area.

Method of Work

Task Force members met with numerous interviewees, both in large Task Force meetings and in smaller groups, to gain understanding of the problems and issues and to obtain the many and often divergent views found among NCI and FDA staff. A list of those interviewed is found in Appendix B. In some instances, interviewees met with the Task Force several times. Interviewees were provided with the charge to the Task Force, a list of Task Force members, and opportunity for prior discussion with staff about expectations in the interviews. A list of Task Force meetings and discussions is included in Appendix C. No verbatim transcripts or recordings of the meetings with the Task Force were made. Summary minutes were kept.

Members reviewed documents, including hearing records and transcripts; memoranda; INDs, records, and letters in the files of NCI and FDA; minutes of meetings; staffing charts; mission and function statements of organizations and public advisory committees concerned with the investigational new drug development process; summaries and suggestions prepared by individual interviewees; newspaper articles; publications in scientific and professional journals; the Memorandum of Understanding (MOU) between FDA and NCI; the Drug Master File (DMF) of NCI; regulations; guidelines; laws pertinent to the investigational new drug development process; operational manuals; draft materials relating to new processes being established; reports of various commissions and other Task Forces -- past and current; contracts and requests for proposals; and investigational reports of FDA, General Accounting Office, and the Department of Health and Human Services (HHS), Inspector General. The group also considered descriptions, special analyses of raw data, and flow charts assembled by NCI and FDA staff. In addition, several cases were studied to elucidate concerns about reported lack of accountability; gaps in communication; ambiguity about roles and responsibilities of institutions, IRBs, NCI investigators, and FDA staff; therapeutic intent; and sanctions.

The general findings and recommendations of the Task Force are presented in Volume I; more detailed background, discussion, and rationale for the findings and recommendations are presented in Volume II.

II. CYTOTOXIC DRUGS - BACKGROUND

Biology of Cytotoxic Drug Treatment of Cancer

A cancer cell differs from a normal host cell in important yet subtle ways. Host defense mechanisms that are mobilized to repel or destroy an invading parasite of another species do not control cancer. Rather, the host nourishes and protects the malignant cells until, as a result of their uncontrolled multiplication, the host is overwhelmed and dies. It is hoped that scientific research eventually will uncover the basic nature of the malignant transformation and that this knowledge will make it possible to control cancer in a rational way, perhaps even to "cure" the cancer cell by reversing the process of transformation. With the present state-of-the-art, the approach to saving the host from cancer is to remove the cancer physically, or to kill every cell of a malignancy that has spread and cannot be treated locally.

While most drugs have their effect by chemically modifying some physiologic process in the host and producing reversible modifications that will disappear in time if the drug is withdrawn, cytotoxic drugs operate by killing cells, obviously an irreversible process. Many toxic effects can be overcome by replication of surviving cells; but this reversibility is of a different and lesser order of magnitude than occurs, for example, with the reversal of effect when a receptor-blocking antagonist to a neurotransmitter is removed from the system.

There being too little difference between cancer and normal host cells for the biologic defense mechanisms of the host to distinguish them, it is generally held that the discovery of a chemical agent that will be deadly for cancer cells, but innocuous for the host, is unlikely. Rather, one hopes to discover drugs which, because there are quantitative differences in metabolism between cancer and normal cells, will be more toxic to the malignancy than to the host. Skillful use of cytotoxic drugs in cancer necessitates coming close to the margin of disastrous toxicity without crossing it. Only in this way can the last cancer cell, which otherwise would extend the malignant process, be irreversibly inactivated. It is no surprise that the treatment success rate with cytotoxic drugs is still low and that major toxicity is the price when success is achieved.

Historical Development of Cytotoxic Drug Treatment of Cancer

In this century, significant advances in the field of cancer have occurred. In 1900, few patients with serious cancer were cured. Since then, the introduction of surgical resection and radiation treatment has provided increased rates of cure and palliation. Advances in surgical technique and radiation equipment and procedures, as well as in supporting areas of anesthesia, blood transfusions, and antibiotics, have greatly augmented the extent to which surgical and radiation techniques have been applied successfully. Failure of further improvement in cure rates was thought to be due to continued growth of "micrometastases," that is, the growth of small groups of tumor cells that could not be recognized as having already spread beyond the local treatment site. Broad systemic treatment to reach such metastases was recognized as needed to supplement removal of a localized tumor. Models of successful use of antibiotics against infectious diseases and the development of systemic antimalarial drugs suggested the possibility that chemicals whicn could control cancer cells wherever they were located in the body. The discovery in the 1940's and 1950's of two chemicals with some antitumor effect (nitrogen mustard and methotrexate) led the U.S. Congress to authorize $5 million in 1955 for NCI to establish a cancer drug development program.

Once it has been shown in the treatment of choriocarcinoma with methotrexate that permanent cure of metastatic cancer could be obtained by chemical means, the objective of clinical experimentation in cancer chemotherapy was to test the possibility that other types of cancer could also be considered to extend the range of effective drugs available for the purpose. Initially, studies were limited to patients with far advanced metastatic cancer, but as successful experience has been gained, there has been movement toward studying patients who are at risk of developing recurrent tumors from unrecognized micrometastases after surgery or radiotherapy for what appear to be localized tumors. The essence of cancer chemotherapy research is to identify chemicals or other natural substances which destroy tumor cells, i.e., chemicals that are cytotoxic. Since cytotoxic drugs affect both normal and tumor cells, the goal is to identify compounds which are selectively more toxic for tumor cells than for normal host cells. The special value of cytotoxic drugs lies in their ability to reach all areas of the body where they can come in contact with and possibly destroy discrete cancer cells which have spread from the obvious local tumor site. Thus, the role of cytotoxic drug therapy is often adjunctive to surgical or radiation therapy which is directed at local tumors. In more disseminated processes, (e.g., leukemia) cytotoxic drug therapy becomes the prime mode of treatment.

Cancer Survival Statistics

In 1900, few cancer patients with serious cancers were curable by any means. Surgical removal of tumors and draining regional lymph nodes was initiated but was mutilating. Use of X-rays proved too toxic because of dosing problems. By 1925, approximately 20 percent of such cancer patients were curable. Over the next 3 decades improvements in surgical techniques, surgical support (such as blood transfusion and antibiotics), and the development of more powerful X-ray units increased the survival for all cancers to a plateau at about 33 percent. In 1957, cobalt 60 therapeutic units became available, and the first linear accelerator was installed. With better machines, the radiation was less toxic, wider fields could be used, and survival statistics rose to about 37 percent by the 1960's. By the mid 1970's, the number of curable patients increased to approximately 41 percent, representing further improvements in radiation therapy and the additional increment due to patients aided by chemotherapy alone. Surgery became less mutilating, and sophisticated radiotherapy decreased the need for radical surgery. Thus, in 1981, the overall effect of cancer therapy is less toxic because of combined modalities of treatment (integration of surgery, radiation, and/or chemotherapy as primary treatments at the time of diagnosis).

Contribution of Cytotoxic Drugs to Treatment Results

There are now many types of malignancies that can be cured with drugs. Beginning with choriocarcinoma, the list has been expanded to include many forms of leukemia, Hodgkins' disease, cancers of the gonads, and of some endocrine tissues such as the pancreatic islets, Burkitt's tumor, and many more. In addition, there are many forms of cancer, such as cancers of the breast, prostate, and small-cell lung tumors, which only rarely respond entirely, but in which drugs often produce remissions which add years of useful life for a patient who, in earlier times, would have been condemned to a rapidly fatal course. Thus, despite lack of a fundamental understanding of the malignant process and how to reverse it, the experience of the last few decades in the development and use of antineoplastic drugs has led to cautious optimism and a growing conviction that more can be done to help patients who have developed cancer.

An analysis of 1977 data by NCI staff led to estimates of the extent to which cytotoxic drugs are useful. In 1977, 700,000 patients were diagnosed as having the more serious cancers; 200,000 of these presented with evidence of metastatic disease. The other 500,000 were diagnosed as having "apparently localized" disease; 280,000 could be expected to remain free of tumor with use of either surgery or radiotherapy alone, and the remaining 220,000 patients would develop recurrent tumors after use of such local treatment alone presumably from unrecognized spread to other body sites that had already occurred at the time of local treatment. This important group of 220,000 patients, if identified, should potentially benefit from cytotoxic drug therapy. (However, there is at present no way to separate these 220,000 patients for treatment from the remainder; to treat them would require treating with cytotoxic drugs the other 280,000 who did not require them.) In addition, of the 200,000 who present with metastatic disease, about 92,000 will benefit to some extent from chemotherapy. Thus, about 200,000 patients with cancer in 1977 were clear candidates for systemic chemotherapy; an additional 220,000 would be if methods could be developed to separate them from the other 280,000 not needing such therapy, or if the toxicity and risks of cytotoxic drugs could be made small enough to allow treatment of all 500,000 patients presenting without evidence of metastases. It is estimated that about 46,000 patients per year are cured or have significant benefit from cancer chemotherapy.

Expectations From New Treatment Modalities

In the cancer treatment field, combinations of therapy have taken stronghold. Just as cytotoxic drug treatment complements local treatment such as surgery and radiation, still other complementary therapeutic modalities may be used in the future. Currently, there is a program to develop and establish biologic response modifiers which involves testing of less toxic natural substances such as interferon, thymotoxin, and monoclonal antibodies. There is, in addition, development of radiosensitizer drugs and radioprotector drugs. New radiotherapy programs will involve particle radiotherapy (e.g., neutron generators). Only future clinical studies will determine how the role of cytotoxic drugs will be altered by these new treatment modalities.

The Cytotoxic Drug Development Program of NCI

In spite of the massive dimensions of the cancer problem in America (over 1000 cancer deaths per day), cytotoxic antineoplastic drugs have not been widely developed and marketed by the pharmaceutical companies (and hence are in the "orphan" category, for the most part). Even the better cytotoxic

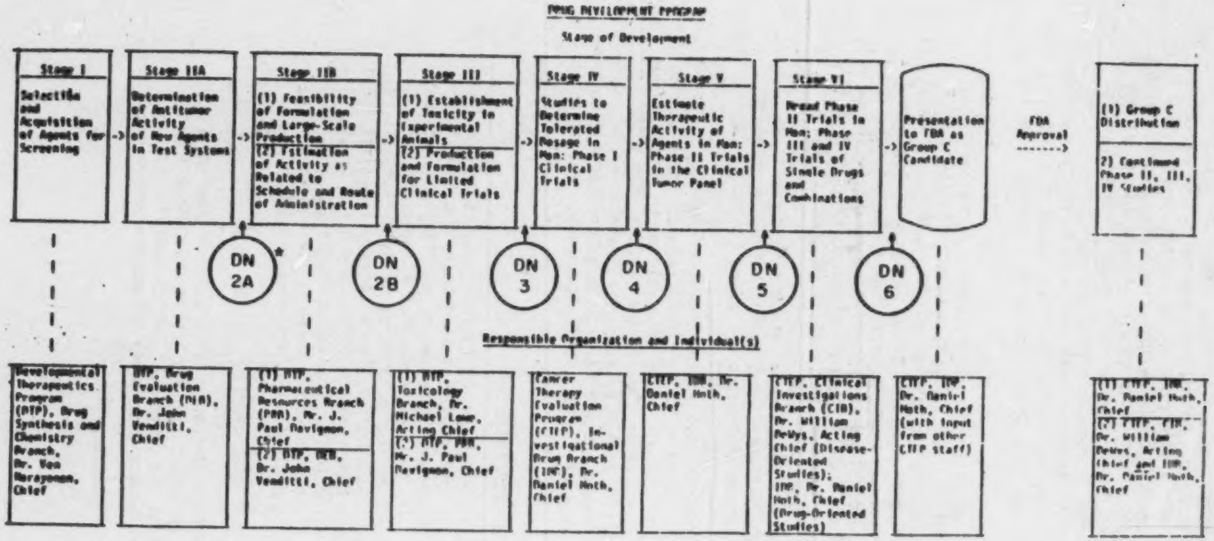

DRUG DEVELOPMENT PROGRAM
Stage of Development
Stage I
Selection and Acquisition of Agents for Screening
Stage IIA
Determination of Antitumor Activity of New Agents in Test Systems
Stage IIB
(1) Feasibility of Formulation and Large-Scale Production
(2) Estimation of Activity as Related to Schedule and Route of Administration
Stage III
(1) Establishment of Toxicity in Experimental Animals
(2) Production and Formulation for Limited Clinical Trials
Stage IV
Studies to Determine Tolerated Dosage in Man: Phase I Clinical Trials
Stage V
Estimate Therapeutic Activity of Agents in Man: Phase II Trials in the Clinical Tumor Panel
Stage VI
Broad Phase II Trials in Man; Phase III and IV Trials of Single Drugs and Combinations
Presentation to FDA as Group C Candidate
FDA Approval
(1) Group C Distribution
2) Continued Phase II, III, IV Studies
DN 2A *
DN 2B
DN 3
DN 4
DN 5
DN 6
Responsible Organization and Individual(s)
Developmental Therapeutics Program (DTP), Drug Synthesis and Chemistry Branch, Dr. Ven Narayanan, Chief
DTP, Drug Evaluation Branch (DEB), Dr. John Venditti, Chief
(1) DTP, Pharmaceutical Resources Branch (PRB), Mr. J. Paul Davignon, Chief
(2) DTP, DEB, Dr. John Venditti, Chief
(1) DTP, Toxicology Branch, Dr. Michael Lowe, Acting Chief
(2) DTP, PRB, Mr. J. Paul Davignon, Chief
Cancer Therapy Evaluation Program (CTEP), Investigational Drug Branch (IDB), Dr. Daniel Hoth, Chief
CTEP, IDB, Dr. Daniel Hoth, Chief
CTEP, Clinical Investigations Branch (CIB), Dr. William DeWys, Acting Chief (Disease-Oriented Studies); IDB, Dr. Daniel Hoth, Chief (Drug-Oriented Studies)
CTEP, IDB, Dr. Daniel Hoth, Chief (with input from other CTEP staff)
(1) CTEP, IDB, Dr. Daniel Hoth, Chief
(2) CTEP, CIB, Dr. William DeWys, Acting Chief and IDB, Dr. Daniel Hoth, Chief

Figure 1

National Cancer Institute Drug Development Program

NCI
12/81

* DN = Decision Network points

drugs, so far, are not good, and those that are clinically active may be superseded rapidly by newer drugs. There are over 100 histopathologically different types of cancer, and a drug that is active in one type may be useless in all other cancers. Therefore, despite a drug market approaching $300 million annually, the market potential of any single cytotoxic drug is likely to remain small. These factors have led the American people, through Congress, to mandate development of these drugs as a publicly-supported venture through NCI. The pressure for rapid progress has been intensified by the optimism resulting from success in certain (unfortunately not the most common) types of cancer, and is reflected in the rapid escalation of the NCI budget during the 1970's.

For the past 25 years, the NCI cytotoxic drug development program has encompassed a wide range of activities -- from identification of potentially useful materials through clinical testing and into general medical practice.

NCI has developed a detailed Decision Network (DN) process for moving a candidate anticancer agent from the initial identification stage through clinical evaluation. The steps in this process are presented in Figure 1.

The Screening Program

Drug development begins with the screening of a wide variety of agents to identify their activity in panels of experimental animal tumors and human tumor tissues. There are two parts to the screening processes -- a "prescreen" testing of compounds in one mouse model, and a more elaborate and extensive "screen" in which the active drug is tested in a panel of several mouse tumors. If found to be active against experimental tumors, the materials undergo large scale production and formulation both for more detailed toxicologic studies in animals and for therapeutic clinical trials.

From 1955 to 1975, a total of 250,000 compounds were screened. Compounds were acquired from the pharmaceutical industry, universities, research institutes, government agencies, and NCI's own intramural laboratories. This was augmented by literature review to select drugs on the basis of relevant chemical, biochemical, pharmacologic, and biologic criteria. Prior to 1975, the prescreen model used was rodents bearing the L1210 leukemia or a variety of other transplanted tumors. This model, however, failed to uncover some important clinically useful drugs. Further, there was concern that it might not uncover new classes of drugs that might be effective. In 1975, a more sensitive mouse P388 leukemia system was substituted for the L1210 model. This system measures the effect of drugs on survival after one million malignant cells are injected peritoneally. The screening approach was changed to test drugs against matched pairs of tumors of the same organ system, i.e., human tumors growing in immune deficient (athymic or nude) mice and corresponding transplantable murine tumors of the same organ. Concomitantly, the number of compounds screened was reduced to approximately 15,000 annually. In 1981, approximately 2,500 compounds were screened.

NCI characterized the changes in the screening protocol as a series of experiments. The goal was to develop a new system and to answer the following questions: (1) would new types of drugs be developed? (the underlying assumption being that new modes of action might be associated with better results); (2) would a new system predict for a specific human tumor type from the results of drug treatment of experimental tumors of the same organ?; (3) would human tumor cells transplanted to mice models be more predictive for man than rodent tumors cells?; and (4) would those results be organ specific? The current screening technique using the more sensitive in vivo mouse P388 leukemia system yields a higher percent of active compounds, i.e., compounds that show some antitumor activity in animal models. Thus, the more sensitive system applied to 15,000 compounds per year produces the same number of active candidates for the next stage of the development process as did the previous less sensitive L1210 leukemia mouse applied annually to much larger numbers. It will be difficult to determine if the new screening process will be more effective and/or efficient than the old for identifying drugs which will be useful in treating human cancer.

Recognizing the experimental and unsure nature of the relationship between animal screening tests and potential clinical usefulness, NCI has opened other pathways for products to be included in the testing program. Thus, a bypass of screening is allowed for compounds that have been shown to be active in other screening programs (done under the aegis of organizations other than NCI); that exhibit pertinent biochemical and/or other biologic properties; or that have been demonstrated in other countries to have some human effect.

The prescreening program goal is to submit between 500 to 1,000 compounds per year to the broader animal tumor panel for evaluation, a number which is derived on the practical programmatic grounds of being the number that can be handled adequately with available resources. The spectrum of tumors in the screening panel includes the following: transplantable lung, colon, and breast tumors of mice which are matched by corresponding human tumor xenografts in nude mice; and previously used mouse tumors such as the L1210 leukemia and the 16B melanoma. Antitumor activity in any one or more of these tumors is enough to move a compound to the clinical trial phase. Ultimate utility of this screening approach will be evaluated as feedback from later clinical trials becomes known.

Another part of the drug development program experiment is to explore in vitro tests that will predict human toxicity and/or therapeutic effect. The prescreen mechanism using P388 mouse leukemia systems costs $184 to decide if a compound is inactive. If active in this test, the compound is moved to testing in the panel of eight tumors, the strategy being to have experimental systems for testing of solid tumors as well as leukemia. It costs about $10,000 to demonstrate that a compound is negative in the eight tumor panels. Thus, an inexpensive in vitro prescreening test is needed because it would weed out the vast majority of inactive compounds more inexpensively and rapidly while potentially maintaining acceptable predicative value. To date, little correlation has been found between such in vitro tests with human effects. New and different in vitro tests are being studied.

The subsequent toxicology testing costs approximates $260,000 for each drug.

Toxicity Testing

Prior to administration of any drug to humans, it is tested in animals to determine that it does not have unacceptable toxicity. Cytotoxic drugs constitute an unusual class because by definition they are toxic, and significant degrees of toxicity are expected and considered acceptable. For these drugs, the purposes of animal testing are to identify a safe initial dose for humans, to identify types of toxicity that might be expected to occur in humans, to determine whether cumulative toxicity might be expected from repeated doses, and to assess whether toxicities are reversible. The characteristics of animal testing and the special dilemmas associated with interpreting their meaning for human use will be discussed in considerable detail in Section V, Toxicology Protocol.

The Clinical Testing Program

1. Phases I, II, and III Clinical Trials

For most classes of drugs, the process for testing and evaluation in humans, after having demonstrated promise of efficacy in laboratory animals and other model systems and after having been shown not to be unacceptably toxic, is usually divided conceptually into three phases. These phases are defined in Title CFR 21, Part 312, the FDA regulations for new drugs for investigational use. Phase I covers the first uses in man, there having been until then only laboratory and animal experience. The objectives are to determine human toxicity, metabolism, absorption, elimination, preferred route of administration, and safe dosage range.

In Phase II, the first effort is made using information derived from Phase I to measure the efficacy of the new drug in treating the target disease. Phase III is the stage of clinical trials which requires study of a large number of patients under conditions similar to the expected ultimate use of the drug in clinical practice. Phase III studies must be extensive enough to permit conclusions to be drawn regarding the risks and benefits to be expected from clinical use of the drug. Comparison is then made of these with the risks and benefits of whatever form of treatment is the currently accepted norm for the target disease or condition. Ordinarily, at the conclusion of a Phase III study, the data on a successful new drug will be submitted to FDA as part of a New Drug Application (NDA) for marketing of the drug. "Phase IV," a term not defined in FDA regulations, is sometimes used to refer to epidemiologic studies done on marketed drugs (post-marketing surveillance). It should be noted that, while there are important differences between the scientific objectives of Phases I, II, and III in drug testing, the operational dividing lines are not absolutely sharp. FDA regulations specify that Phases I and II may overlap. Phase II is in many respects a feasibility study for Phase III, and the last patients treated in a Phase II study may have received precisely the same treatment as that given to larger numbers of individuals under Phase III.

The characteristics of Phases I, II, and III are different for cytotoxic drugs from those for other classes of drugs.

2. Groups A, B, and C Drugs

For purposes of distribution by NCI of the cytotoxic agents to the large and complex system for clinical testing, drugs are classified as A, B, or C or their subcategories -- categories which cut across the previously defined Phases I, II, or III because of the differences between cytotoxic and other classes of drugs. They are characterized as follows:

Group A_I

"A one" is the designation for drugs undergoing Phase I studies to identify types and severity of the drug's toxicities, to identify the maximally tolerated dose for specific dosing schedules, and to determine the clinical pharmacology and pharmacokinetics.

Group A_{II}

"A two" is the designation for drugs undergoing early, single agent Phase II studies in six to 10 specific signal tumors to estimate the frequency of clinical response and safety of the drug.

Group B Drugs

Group B is the designation for drugs undergoing both subsequent single agent Phase II trials and late Phase II multiple-agent or multiple-modality studies in signal tumor panels to estimate effectiveness. Also, Phase III trials comparing the efficacy of one therapeutic plan, including the investigational new drug, against another therapeutic plan are carried out under the Group B designation. The focus of the clinical trials is determining the role of the drug in the therapy of specific neoplastic diseases.

Group C Drugs

Group C are those drugs which have (1) been found to have a role in the treatment of a specific tumor type in more than one study; (2) have not (yet) been sponsored by a pharmaceutical firm and obtained NDA approval and marketing; and (3) which, in the interim, are allowed a controlled distribution to qualified physicians for treatment of specific cancers. A secondary purpose of this distribution is to acquire more information on safety of the drug being used as it will be used in clinical practice after marketing.

3. Size of the Clinical Testing Program

The extensive clinical testing program for cytotoxic drugs supported by NCI and differences from testing other classes of drugs will be described in Section VI, Clinical Trials. Its size is indicated by the following: the number of new patients being studied in protocols during a year is approximately 37,000; approximately 100 requests for drugs are received per day; approximately 5000 physicians are registered to receive the drugs for treating patients at any time; and, approximately 1000 requests per year for a "compassionate IND," (special exception) drug use are received by NCI. (See Section VII, Investigational New Drugs and Investigators.)

4. Cytotoxic Drug Distribution and Cancer Treatment Plan

Drugs are distributed to investigators according to the kinds of studies they perform. The Current Cytotoxic Drug Distribution and Cancer Treatment Plan is illustrated in Figure 2. Briefly, Phase I and early Phase II studies

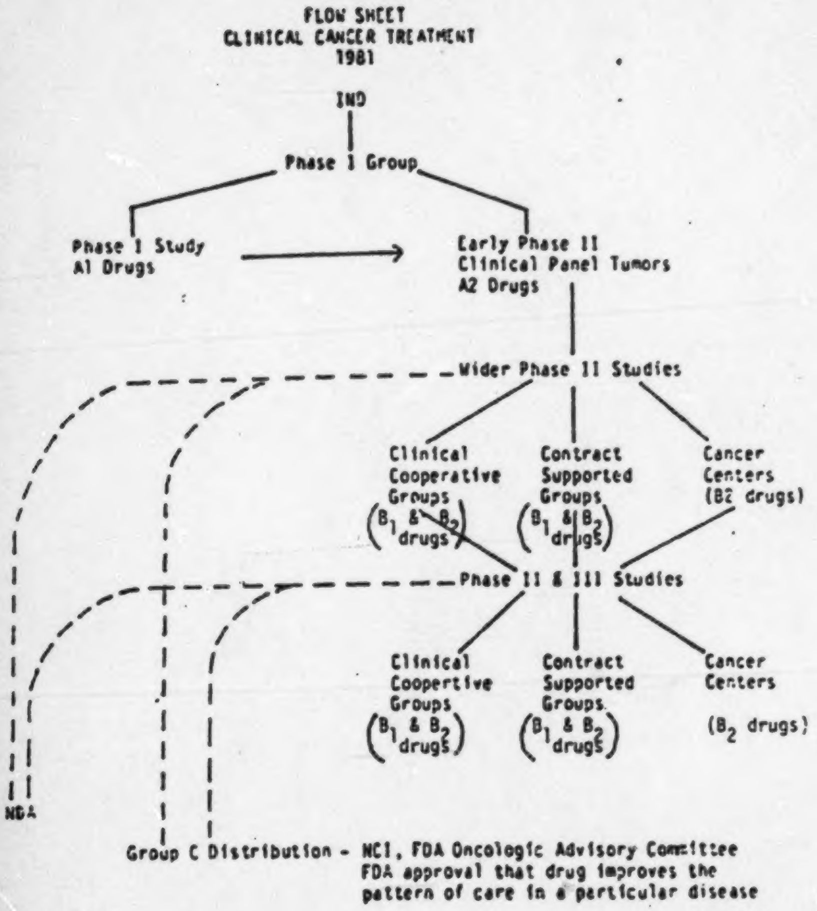

FLOW SHEET
CLINICAL CANCER TREATMENT
1981
IND
Phase I Group
Phase I Study
A1 Drugs
Early Phase II
Clinical Panel Tumors
A2 Drugs
Wider Phase II Studies
Clinical Cooperative Groups
(B_1 & B_2 drugs)
Contract Supported Groups
(B_1 & B_2 drugs)
Cancer Centers
(B2 drugs)
Phase II & III Studies
Clinical Coopertive Groups
(B_1 & B_2 drugs)
Contract Supported Groups
(B_1 & B_2 drugs)
Cancer Centers
(B_2 drugs)
NDA
Group C Distribution - NCI, FDA Oncologic Advisory Committee
FDA approval that drug improves the
pattern of care in a particular disease

Figure 2. Current Cytotoxic Drug Distribution and Cancer Treatment Plan

NCI
12/81

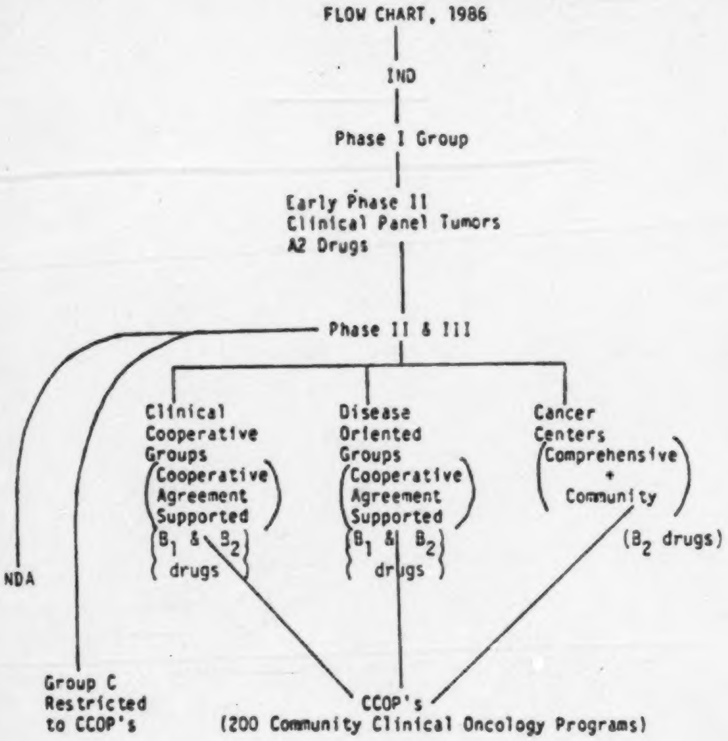

FLOW CHART, 1986
IND
Phase I Group
Early Phase II
Clinical Panel Tumors
A2 Drugs
Phase II & III
Clinical
Cooperative
Groups
Cooperative
Agreement
Supported
B_1 & B_2
drugs
Disease
Oriented
Groups
Cooperative
Agreement
Supported
B_1 & B_2
drugs
Cancer
Centers
Comprehensive
+
Community
(B_2 drugs)
NDA
Group C
Restricted
to CCOP's
CCOP's
(200 Community Clinical Oncology Programs)

Figure 3

Figure 3. Planned 1986 Cytotoxic Drug Distribution and Cancer Treatment Plan

NCI
12/81

are restricted to Phase I Working Group Members (primarily Phase I contractors and NCI intramural investigators). When a drug is ready for wider Phase II and Phase III studies, it is made available to the clinical cooperative groups, the contract-supported disease-oriented groups, and the cancer centers. When a drug is approved by FDA for Group C, it is also made available with guidelines for use to individual physicians who have filed with NCI registration form FD 1573, Statement of Investigator.

The future NCI drug distribution and cancer treatment plan is indicated in Figure 3. No major changes are planned in the distribution of drugs for Phase I and early Phase II studies. The major differences projected for 1986 relate to the institutions that will be involved in the proposed Community Clinical Oncology Program (CCOP). Plans are to eliminate distribution of Group C drugs to individual physicians and to utilize instead the CCOP investigators. The CCOP institutions will participate in certain Phase II and Phase III studies with contractors, cooperative groups, centers, and other treatment groups.

Current Scope of NCI Cytotoxic Drug Development Program

NCI is presently sponsor for about 70 cytotoxic drug INDs which are in various stages of clinical testing. Because cancer constitutes more than 100 biologically different tumors, individual cytotoxic drugs often are in different stages of testing simultaneously for more than one kind of tumor.

Today, 29 cytotoxic drugs have obtained NDA approval and are marketed for treatment of cancer. NCI has played an important role in the research and development of 19 of these anticancer drugs. The scope of the NCI effort is illustrated by the facts that only one of 5,000 compounds screened reaches the stage of clinical evaluation and only one of 50,000 drugs screened in animals for anticancer activity reaches the cancer patient through the marketplace. Between 1975 and 1981, 30 INDs were opened for cytotoxic drugs, and one inactive IND was reopened.

Eight drugs have been or are in the process of being tested in all the panel tumors (Leukemia, Lymphoma, Lung, Breast, Colon, and Melanoma). Five additional drugs have been tested in five of the six tumor panels. Also, 11 have been tested in tumors other than the panel. The most frequent nonpanel tumors tested have been sarcomas, and ovarian, renal, and brain tumors.

III. A REVIEW OF TWO CASES CONCERNING NCI'S ANTICANCER DRUG PROGRAM

A number of cases came to the Task Force's attention in which it was alleged that researchers and/or administrators acted improperly in carrying out their responsibilities under the NCI drug development program. These cases do not themselves prove that there are deficiencies in the program. They at least raise questions, however, as to whether there are shortcomings that need to be addressed in such areas as approval of new protocols; reporting of ADRs in ongoing protocols; training of researchers and administrators; monitoring of researchers by NCI, FDA, and institutions; protection of human subjects; and control of drug distribution.

To assist in carrying out its charge, the Task Force examined a number of cases aired in Congressional hearings on NCI's drug development program. In so doing, the Task Force did not consider it necessary, nor did it have the detailed information or time, to resolve factual disputes or develop definitive chronologies. The Task Force recognized the difficulty in generalizing from individual incidents which might simply reflect isolated aberrations rather than fundamental problems. Nevertheless, the Task Force considered these cases as important guideposts in identifying areas of the drug development program to be scrutinized and evaluated. Furthermore, the extensive interviews heard by the Task Force have indicated that the preceding problems encountered in the cases are not isolated.

Without attempting to catalog each case, two deserve specific mention because they not only have been widely publicized, but because they point up most of the issues raised by the entire range of specific situations that have come to the Task Force's attention.

Methyl CCNU and Renal Insufficiency

As far as the Task Force can determine from the information supplied to it, Methyl CCNU (MeCCNU) was an anticancer drug developed by NCI in the late 1960's. Preclinical studies in monkeys and dogs showed the drug caused acute renal insufficiency. In 1971, NCI filed an IND with FDA and began Phase I trials with MeCCNU. At that time, NCI distributed a brochure to investigators which recounted the results of the animal studies. It is not clear whether or not this information was passed on by investigators to their patients. Phase I trials were completed by early 1972 with no evidence of renal insufficiency being noted. During the next 6 years, the drug proceeded through a series of Phases II and III trials, again with no renal insufficiency being noted. In 1976, with the approval of FDA, NCI made MeCCNU available for wider distribution and use in treating various forms of cancer. In August 1977, NCI received a report of renal damage in a 5-year-old child who had been on the medication for 17 months.*

---

* Task Force members were advised of possible reports of renal insufficiency prior to this time, but were unable to confirm whether such reports actually occurred and, if so, to whom they were made.

Several more cases of chronic renal insufficiency in children were reported in mid-1978. At that time, NCI decided to study the matter further before contacting FDA, to ensure that the renal insufficiency was indeed related to MeCCNU. To make this assessment, NCI contacted all its investigators using the drug for the purpose of seeking further information. As a result, in late 1978, a number of added cases were discovered. This led NCI's Adverse Drug Reaction Committee (ADRC) to conclude in February 1979 that the renal insufficiency was associated with MeCCNU, and, almost immediately NCI filed an ADR report with FDA. NCI also then advised all investigators on the MeCCNU distribution list of these findings and requested reporting of any additional cases. In addition, NCI's MeCCNU protocol was amended to incorporate the findings. In July 1979, FDA inspectors conducted the first of several visits to NCI regarding MeCCNU. These contacts have led to modification in NCI procedures for reporting ADRs to FDA. No sanctions were imposed against investigators who failed to report ADRs to NCI in a timely manner.

5 Methyl THHF

In 1978, NCI supplied a scientist at M.D. Anderson Hospital with an experimental compound, 5 Methyltetrahydrohomofolate (5 MeTHHF), for use in animal pharmacology studies. Between March and July 1980, the scientist and his collaborators carried out clinical pharmacology studies on six patients using 5 MeTHHF. Although M.D. Anderson had received preliminary approval from NCI for such a study, it had not been approved by the M.D. Anderson IRB, nor did M.D. Anderson have an FDA-approved IND for the study. In late April 1981, the M.D. Anderson scientist presented the results of his study at a professional meeting. In mid-June 1981, the study came to the attention of NCI officials who immediately contacted FDA and sent a site visit team to M.D. Anderson. The team verified the facts and made a number of recommendations including the following: termination of the contract under which the study was conducted; recovery of federal funds used to support the study; modification of M.D. Anderson procedures to ensure better compliance with NIH and FDA requirements; and removal of the scientist from leadership responsibility for federally-supported research. These recommendations were adopted by the Director of NCI and NIH, with the added stipulations that for 2 years the scientist's infractions be brought to the attention of committees considering applications by him for NIH support, and that, for the same period, he not be allowed to serve on NIH advisory committees.

In themselves, these and other similar cases that have come to the Task Force's attention, do not prove that there are deficiencies in the NCI drug development program. They do, however, indicate failures in the specific instances involved which raise more general questions as to the adequacy of -

- procedures for reporting new clinical protocols and ADRs in ongoing clinical protocols;
- programs for training researchers and administrators as to their reporting responsibilities;

- monitoring of researchers by NCI, FDA, and their own institutions;
- procedures for ensuring that human subjects are protected;
- controls on distribution of experimental drugs;
- sanctions for failure to follow established procedures.

In subsequent sections in Volumes I and II, the Task Force will systematically examine the NCI drug development program as it exists today, identify strengths and weaknesses, and make recommendations for change. In so doing, the Task Force will attempt to be responsive to questions raised by the MeCCNU, 5 MeTHHF, and other specific cases. NCI and FDA, however, are aware that there have been shortcomings in the program, and they have already taken significant steps to alleviate them. It is hoped that, to the extent the individual cases referred to above reflect common problems in the program, the changes already instituted, plus such others as may be adopted in response to this report, will reduce the likelihood of similar cases occurring in the future.

IV. MEMORANDUM OF UNDERSTANDING

A Memorandum of Understanding (MOU) relative to anticancer drug development, signed by the Director, NIH, and the Commissioner of Food and Drugs, became effective on February 5, 1979, and was published in the Federal Register on May 1, 1979. (See Appendix F.) The prologue noted that DCT, NCI and BD, FDA had a considerable ongoing informal interchange. To supplement and strengthen that direct working relationship, it was believed that a formal MOU was desirable.

The MOU designated the Director, DCT, as the primary NIH contact on matters of policy relative to anticancer drug development. The FDA designee is the Associate Director for New Drug Evaluation, BD. Individual staff members of those offices were encouraged to interact with their counterparts as appropriate on day-to-day matters. DCT agreed to designate individuals to serve as liaison to FDA's Oncologic Drugs Advisory Committee and to attend other meetings as necessary. BD agreed to designate appropriate staff as liaison to the DN Phase I Working Group, the New Drug Liaison Committee, and other meetings as necessary. DCT agreed to transmit to FDA relevant information such as the Cancer Treatment Report and copies of minutes of pertinent meetings of internal liaison groups. However, such transmittals were not to be a substitute for the required annual progress report required for each IND.

In its role as sponsor of INDs, the DCT agreed to comply with all applicable regulations and legal requirements. BD, recognizing the position occupied by DCT in anticancer drug development, agreed to assist DCT in the furtherance of its objectives to the degree permitted by regulations and law.

If there is disagreement on matters related to the regulation by FDA of an IND sponsored by NCI, the matter is to be brought to the attention of the Director, NCI, and the Director, BD, for joint resolution. The next level of appeal is the Commissioner of Food and Drugs, and the Director, NIH. Absent resolution, final determination rests with the Commissioner of Food and Drugs.

DCT agreed to maintain and BD to accept and house a Drug Master File (DMF). The DMF would include information applicable to all anticancer investigational drugs sponsored by DCT. That information could thus be incorporated by reference to the DMF into all INDs for anticancer drugs sponsored by DCT. The major purpose of the DMF, therefore, is to avoid duplicating material in each new IND for which DCT is sponsor. Reference is made in the IND to specific material in the DMF of the sponsor. Proposed revisions to the DMF, according to the MOU, would be submitted first in draft form by DCT to BD for comment. DCT would keep the file current and make changes as requested by BD. On or about January 1 of each year, DCT agreed to forward to BD a list of documents in the DMF and a certification of their currency and accuracy.

The NCI DMF actually started December 10, 1976. Considerable bilateral effort had been underway to bring the NCI IND program in line with FDA regulations. It was agreed an MOU would strengthen that effort, and ample opportunity was provided throughout both organizations for staff comments in its development. The initial draft was written in NCI, since it had been the organization to suggest such a mechanism, and comment was furnished by FDA.

There is at least one other comparable MOU between FDA and another governmental organization. The Federal Register of November 29, 1974, published an MOU between the Department of Defense (DOD) and FDA on DOD procedures in the development of INDs. It contains a description of the necessary DOD review boards and emphasizes the protecton of human subjects throughout the clinical testing processes. It also contains unique elements to guarantee the integrity of national security.

Management of both DCT and BD state that the MOU has worked well and is continuing to work well. Both organizations have recently reviewed the MOU, and neither proposes any change in content at this time. There is agreement that the document should permit changes or additions at any time. Most discussions, in all quarters, have centered around the contents and use of the DMF, as discussed below, not on the MOU itself. BD feels that continuation of the MOU is important because, if it were not for the current system, including the DMF, the onslaught of IND paperwork being forwarded by NCI would be overwhelming.

FDA has utilized the DMF concept for approximately 40 years. There are two major reasons for the existence of DMFs. The first, is the protection of trade secrets. A drug company may file information about the chemistry and pharmacology of a particular chemical for the information of FDA alone. Subsequently, licensed producers of that drug may file, in separate DMFs, information about color additives, packaging procedures, and so on. Consequently, each of the companies involved may utilize its portion of the information for a subsequent NDA without violating the confidentiality of information of any other company. The second reason, and the one most important in regard to the current review, is to avoid the redundancy of submitting the same material many times over for each of several INDs or NDAs.

There are more than 4,000 DMFs on file in FDA. Once established, a DMF holder requests the FDA to refer to it on behalf of an applicant/sponsor. The individual sponsor determines what to put in the DMF. The contents of DMFs are neither approved nor disapproved. They are, however, "accepted" and the applicant/sponsor is so notified for both the original acceptance and the acceptance of any subsequent information submitted to the DMF. If the material is judged by BD not essential nor germane to any pending or subsequently expected INDs or NDAs, the material is rejected and the applicant so notified. FDA guidelines suggest it would be beneficial for an applicant/sponsor who holds a DMF to assure FDA annually by letter that the information in the file is current -- including a revised index identifying the active status of each section and any deletions, changes, or additions made. A DMF not annually updated in this fashion, however, is not discarded. At no time is the DMF purged of information since all the cumulative material contained may be of historical or legal significance.

The size and contents of DMFs vary considerably. Most commonly they contain basic information regarding an organization's personnel and their responsibilities, including curricula vitae and organizational charts. Other items may include production and processing procedures, laboratory controls, product stability, and expiration dating information. The inclusion of generic protocols for animal and clinical studies are the exception and are unique to the NCI DMF.

The DMF of NCI (DMF 2803) now consists of nine volumes. The contents include -

- Screening methods used to determine anticancer activity;
- Description of preclinical toxicity testing methods;
- NCI's quality control procedures for the manufacture, screening, and toxicological testing of compounds;
- Organizational chart of DCT, NCI;
- *Curricula vitae* of NCI staff;
- List of the cancer centers;
- Definition and description of Groups A, B, and C drugs;
- Plan and procedures for clinical trials data reporting by cancer centers, including monitoring and the reporting of ADRs;
- Description of the decision-making criteria at NCI for the initiation and continuation of clinical trials;
- Responsibility of DCT with respect to preparation of INDs and reporting of data.

Although the MOU provides for yearly documentation that the DMF is current, BD and NCI believe it is not needed because the file has frequent reviews and revisions. A major update was accomplished voluntarily by NCI on May 7, 1981, with a submission containing such items as anticancer screens, Toxicology Protocol update, and quality control procedures. On October 16, 1981, NCI submitted to the DMF data from lethality and toxicology studies for six IND drugs such a methotrexate and 5-fluorouracil. This is part of a 20-drug study being done under contract to provide data supportive to the scientific basis of NCI's preclinical toxicology program. In October 1981, BD reviewed the NCI DMF and requested certain revisions, primarily relative to ADRs, i.e., a description of where reporting responsibilities rest currently, changes in the ADR flow chart, and a clarification that serious ADRs should be reported to FDA within 15 days. These changes and additions were forwarded by NCI to BD in November 1981 and are under review prior to being entered into the DMF. On December 15, 1981, NCI submitted a proposed revision of the Toxicology Protocol.

Two aspects of NCI's DMF that differ from other DMFs are its large size and its dealing with only a single class of drugs. The usual industrial IND sponsor DMF provides information just on physical plant, quality control, and so on. Most sponsors have several DMFs, each containing one to four such elements. NCI's DMF is manageable, in spite of its large size, because of its volume numbering system. Although the April 1981 revision of the Toxicology Protocol in the DMF is accompanied by a letter providing an index to that section, the DMF has no overall index making it a difficult reference source for frequent use. Other governmental units have DMFs, although less comprehensive than NCI's. The Veterans Administration has three files, covering chemotherapy, psychiatric disease, and the curricula vitae of investigators. DOD has two files. Other investigators of cancer drugs which act as sponsors have DMFs which are much less extensive than that of NCI. For example, the Sloan Kettering Institute has a single DMF which includes only clinical investigators' curricula vitae.

In August 1980, an individual staff member of BD requested the Commissioner of Food and Drugs to review the decision to accept the NCI's DMF. In the absence of a response, the request was repeated in June 1981. The issue of concern was whether the acceptance of DMF materials constituted endorsement of the content, even though FDA policy was and continues to be that there is no implication of endorsement. The only agreement is to keep DMFs on file for future use when considering individual INDs and NDAs.

The Task Force believes that the MOU does not significantly alter the usual BD/sponsor relationship. The MOU is useful to FDA because it can improve understanding by BD personnel of the special features of the NCI cytotoxic drug development program, particularly with regard to clinical trials. Additionally, the MOU makes it clear that NCI is subject to the regulatory actions of FDA. It has been stated that, prior to the MOU, some staff in FDA wanted a firmer stance of regulation toward NCI, whereas some NCI staff wanted more independence from FDA.

Staff disagreements, for example with regard to the toxicology guidelines, or other substantive matters can be addressed directly without questioning the regulator-regulatee relationship between the institutions. Thus, the MOU has contributed to better understanding between NCI and FDA of their respective roles.

Staff perceptions of the efficacy of the cooperative liaison called for in MOU are uneven. The problems, however, relate to the implementation of the MOU, not the document itself. The Task Force does not find a need for change in the MOU and concludes that the MOU is an appropriate document in which future management and operational statements may be incorporated in the attempt by NCI and FDA to maintain a sound and responsive program for anticancer development.

V. TOXICOLOGY PROTOCOL

After a chemical has been shown to be active against tumor cells in laboratory testing and before it is tested in humans, the toxicity of the chemical is tested in animals. Among the purposes of this testing are to identify a safe initial dose for humans, to identify types of toxicity that might be expected to occur in humans, to determine whether cumulative toxicity might be expected from repeated doses, and to assess whether toxicities are reversible.

The process by which NCI tests the toxicity of new potentially active cytotoxic drugs in animals has evolved over the last decade and is expected to continue to evolve. In January 1973 NCI published a set of procedures for such testing that included estimation of the LD_{50} in mice, single-dose (x1) study in dogs, five daily dose (x5) study in dogs, five daily dose study in monkeys and study of intermittent dosing (five days on drug, nine off, five on, nine off, five on) of dogs.

A. Shortcomings of 1973 Protocol

Based on the experience of several years of use of the 1973 Protocol, several problems with it were identified. The studies in monkeys had been intended primarily to identify types of toxicity that might be anticipated to occur in humans, but comparison of studies in dogs and monkeys with subsequent events in humans showed that the monkey studies added little to the information available from dogs. The increasing cost and scarcity of monkeys provided additional incentive to curtail toxicity testing in that species. On May 11, 1979, FDA agreed to NCI's proposal to stop use of monkeys for preclinical toxicity studies.

The multiplicity of tests in animals and the requirement that histopathology of the large animals be completed before human testing began resulted in a minimum interval of nine months from the initiation of animal toxicity studies to the start of Phase I testing in humans. In the hope that some of the candidate drugs would be useful clinically, shortening of this interval was considered desirable. Some (but not all) persons felt that the study of intermittent doses in dogs added little information on cumulative toxicities in humans. This kind of study was thought to contribute to the long interval required for animal toxicity testing.

Another effect desired was a reduction in cost of animal toxicity testing. The average cost of toxicity testing was estimated as $351,000. Although this cost apparently was never a limiting factor in the testing of cytotoxic agents, one could envision other good uses to which that money might go if toxicity testing were less expensive. Further, the expense might indeed limit the number of drugs that could be tested in the future. Another advantage of a less arduous and less expensive testing scheme (assuming no meaningful decrease in information as to safety for humans) was that industry would be more likely to enter the cytotoxic drug development field.

B. Deciding on a New Toxicology Protocol; The Process

In drafting a new Toxicology Protocol, staff of NCI critically reviewed the value of previous animal toxicity studies in predicting safe doses and organ toxicities in cancer patients. That these analyses were subjected to the critical scrutiny of experts in the field is seen in the facts that the Rozencweig* study of the predictive value of animal testing was presented at the Annual Meeting of the American Association for Cancer Research in New Orleans, May 15-19, 1979; that the Guarino study of murine toxicity data was published in June 1979 in Cancer Research**; and that an announcement of NCI's proposals was published in the July 1979 issue of the Division of Cancer Treatment Bulletin, solicting comments from the general oncologic community.

On July 9, 1979, NCI's initial proposal for the new Toxicology Protocol was considered by a special Subcommittee, the Toxicology Guidelines Subcommittee, of FDA's Oncologic Drugs Advisory Committee. The Subcommittee consisted of three medical oncologists and a statistician. To augment their knowledge and broaden the perspective of their deliberations, a toxicologist, a pharmacologist, and an outside oncologist were used as additional consultants. NCI proposed two options to the Subcommittee. Option A, which NCI favored, would have restricted testing to single dose and five daily dose studies in mice, and based the initial human dose and one-tenth the mouse LD_{10} on a mg/m^2 basis. Histopathology or chronic toxicity studies would be done in the dog or mouse only later, when and if the drug were being considered for broader human use as a Group C drug or by approval of an NDA for marketing. Option B would have involved determining the LD_{10} in mice and the "toxic dose low"(TDL) in dogs, and basing the initial human dose on one-third the mouse LD_{10} or one-third the dog TDL (on a mg/m^2 basis), whichever was less. Hematology, clinical chemistries, and gross pathology would be done in both species; tissues would not be studied histologically before early human studies, but would be saved for histopathology which would be completed prior to submission of an NDA. The Subcommittee agreed with NCI that the mouse could serve a a predictor of the starting dose in humans (if adequate numbers of mice were tested) and that the single dose and five daily dose regimens were appropriate for determining the LD_{10} from which the human dose was derived. To look for delayed toxicity and reversibility of toxicity, the Subcommittee recommended that animals be observed for at least 28 days, and longer if the animals had not recovered from the acute toxic effects of the treatment. They agreed that hematology, clinical chemistry, and histopathology need not be required in the murine studies, but recommended that such studies be encouraged so that the value of the mouse in predicting qualitative drug toxicity could be determined. The Subcommittee concluded that it was important that an additional species, such as the dog, be tested to assess quantitative as well as qualitative toxicity. Although members of the Subcommittee differed on the utility of dog studies for predicting qualitative toxicity, some thought that such studies (employing doses that produce overt toxicity) might prove useful for specific agents and that their value should be prospectively studied. The initial dose recommended for dogs was one-tenth the mouse LD_{10} (on a mg/m^2 equivalent basis). The Subcommittee recommended that Phase I trials be permitted to start after 60 days observation of dogs given this dose, assuming that this testing confirmed the safety of that dose. The Subcommittee recommended that the histopathology of all dogs be completed prior to initiation of Phase II clinical trials. In the course of its deliberations, the Subcommittee heard and considered the view of Dr. David Richman, a pharmacologist from FDA, who argued that histopathology should be completed prior to Phase I to aid in identifying the clinical monitoring needed in early clinical studies. The Subcommittee also stated that studies of carcinogenicity of all cytotoxic drugs should be initiated and, if possible, completed before approval of the NDA. Similarly, they indicated that testing of teratogenicity and effects on fertility also should be completed by that time.

---

* Rozencweig, Marcel, et.al. "Animal Toxicology for Early Clinical Trials with Anti-Cancer Agents." Cancer Clinical Trials, Vol. 4, 21-28, 1981.

** Guarino, Anthony M., et.al. "Adequacies and Inadequacies of Assessing Murine Toxicity Data with Antineoplastic Agents." Cancer Research, Vol. 39, 2204-2210, 1979.

On October 12, 1979, the deliberations of the Toxicology Guidelines Subcommittee were reviewed by the full Oncologic Drugs Advisory Committee, composed of eight oncologists and two statisticians. It was generally agreed that the Guidelines proposed represented "a reasonable interim approach until such time as there are additional data to support the use of a murine system alone." The only addendum offered was that an appropriate statistical design be used to ensure reliability in the estimation of the mouse LD_{10}, LD_{50} and LD_{90}. The Committee voted to approve the Subcommittee's recommendation unanimously except for one abstention.

At its October 29-30, 1979, meeting the DCT Board of Scientific Counselors (BSC) was told of the approval of the amended Toxicology Protocol by the Oncologic Drugs Advisory Committee. Minutes of a subsequent meeting of the Board suggest that the Board approved the Toxicology Protocol in its 1979 meeting.

Dr. Richard Crout, Director, BD, FDA, notes that because of FDA staff disagreement about the proposed Toxicology Guidelines, extensive discussions ensued within FDA. Dr. Richman concurs, noting that his views "were given airing in considerable detail," especially by Dr. Crout and officials in the Commissioner's office who "sought (him) out to have extremely frank and lengthy discussions."

On February 6, 1980, Dr. Crout approved the new Toxicology Protocol. On March 7, 1980, the Protocol was added to NCI's DMF along with a cover letter that indicated 1) that the value of mouse histopathology would be reviewed two to three years hence, and 2) that the starting human dose would be one-tenth the mouse LD_{10} unless that dose produced frank toxicity in dogs, in which case a lower starting dose would be determined in dogs "as described by the Protocol." The Protocol, however, stated only that, if toxicity were apparent in dogs given one-tenth the mouse LD_{10}, "deescalation will occur after consultation" with the Toxicology Program Office of the contractor to NCI for animal testing. No mention was made in the cover letter or protocol about what findings in the routine animal testing would trigger additional studies of cumulative, delayed or irreversible toxicity. In contrast to the recommendation of the Toxicology Guidelines Subcommittee, the protocol submitted to the DMF did not allow for mice to be observed for more than 28 days if toxicity were still apparent, and made observation of dogs for more than 57-60 days optional.

On March 6, 1980, Dr. Robert S. K. Young, Medical Officer, Division of Oncology and Radiopharmaceutical Drug Products, FDA, submitted a petition to the Commissioner of Food and Drugs to review Dr. Crout's decision. He also submitted a Citizens' Petition to the Hearing Clerk on March 31, 1980, and an amendment to the letter on December 17, 1980. Dr. Young's petitions prompted another internal FDA review of the issues surrounding the revised Toxicology Protocol, producing additional documentation of FDA staff disagreement about some substantive issues. For example, in a memorandum in July or August, 1980, Dr. Marion J. Finkel, Associate Director for New Drug Evaluation, indicated that she favored performing histopathology of dogs prior to initiating Phase I trials and retaining the intermittent dosing of dogs (five-nine-five-nine-five) to look for cumulative toxicity. On October 2, 1980, NCI's BSC again expressed the sentiment that the new Toxicology Protocol was satisfactory, but on March 31, 1981, Dr. Crout formally stayed the implementation of the new Toxicology Guidelines, pending resolution of specific issues.

On April 27, 1981, FDA and NCI staff members met to review accumulating data on nine cytotoxic drugs that had been tested or were being tested under the new Toxicology Protocol. Dr. Finkel indicated that she was convinced from discussions at this meeting that histopathology of dogs need not be completed prior to Phase I trials.

On May 7, 1981, a new version of the Toxicology Protocol was submitted to the DMF. The revisions were minor.

On June 12, 1981, the issue of the Toxicology Protocol was once more presented to the BSC of the DCT. The Board was joined, at this meeting, by two representatives of the President's Cancer Panel, so that they might be familiarized with the process of the Protocol's development. The minutes of that meeting do not indicate that formal approval of the Protocol was requested or given, but no disagreement with the Protocol was recorded.

On July 9, 1981, Dr. Crout determined that the BD should accept the NCI protocol "as providing a sufficient routine approach to obtaining information for the early evaluation of cytotoxic drugs in humans." He emphasized that the Protocol had been developed through a valid, open process; that the testing to estimate the initial starting dose was more extensive under the new Protocol; that histopathology had not been essential in the past for the discovery of toxic effects that would alter Phase I testing; and that studies under the new Guidelines were probably no less sensitive in detecting organ-specific toxicity or cumulative or delayed effects (especially since "the high dose testing in the dogs is likely to be greater than the NCI protocols imply").

On July 24, 1981, at the request of the Commissioner of Food and Drugs, Dr. Hayes, and pending his review, BD placed a clinical hold on INDs submitted by NCI under the new Guidelines. On September 1, 1981, NCI and FDA staff met to discuss the Toxicology Protocol further. Dr. Bruce A. Chabner, Acting Director, DCT, indicated that histopathology of mice and dogs could usually be submitted within 90 days of filing an IND (60 days after starting human studies). A proposed revision of the Protocol -- submitted to FDA October 1, 1981 -- confirmed this intention. NCI also modified the Protocol to make more precise the starting dose in man based on the results in whichever was the more sensitive of the two species, mouse or dog. If one-tenth the mouse LD_{10} was found to cause serious toxicity in the dog, the human equivalent starting dose would be one-third the dose that causes minimal reversible toxicity in dogs. Examples of serious toxicity in dogs were given as death; seizure or coma; bloody diarrhea; shock; irreversible hepatic or renal dysfunction; or changes in hematology parameters that did not return to normal within two weeks. In addition, NCI requested that histopathology of certain organs in the mouse be omitted. As of December 1981, FDA had not yet indicated whether or not it will approve these proposed changes.

On October 5, 1981, the history, rationale and proposed revisions of the Toxicology Protocol were presented to the National Cancer Advisory Board (NCAB). NCAB was not asked to approve the Protocol.

On October 5, 1981, Dr. Hayes approved the May 7, 1981, version of the new Protocol as amplified by FDA staff memoranda and the text of NCI's June 12, 1981, presentation to the BSC; on October 14 he denied Dr. Young's petition on the Toxicology Protocol while acknowledging some areas of valid concern that necessitated changes in the Toxicology Protocol prior to publication for comment in the Federal Register as a prelude to accepting it as FDA Guidelines. The Commissioner indicated that decision rules would be needed to determine whether a drug under study appears to have cumulative effects that need further study prior to Phase I trials. He also indicated that clarification was needed of what constitutes the appearance of a serious or delayed drug effect that would necessitate submission of histopathologic data prior to Phase I studies.

On December 15, 1981, NCI submitted to FDA yet another revision of the Toxicology Protocol. This version included protocols for testing in rats, rabbits, and guinea pigs in special circumstances and specified, at least for some protocols, that failure of dogs to recover from toxicities could be sufficient reason to continue their observation beyond two months. NCI proposed to make the toxicity studies in mice optional, as well as to limit the number of organs on which histopathology would be done. (Previous versions of the new Toxicology Protocol had not stated that the mouse toxicity studies were to be optional, but Dr. Crout indicates that their status as optional was generally understood.) This version did not clearly address Dr. Hayes' concerns about the need to specify those findings that would trigger additional testing before initiation of trials in humans.

C. Deciding on a New Toxicology Protocol; Substantive Considerations

The value of testing the toxicity of cytotoxic drugs in animals rests on the presumptions that the results of that testing will add to our knowledge of the toxicities to be expected in humans and that that knowledge will affect how the testing in humans is conducted. Testing that does not do both can be considered superfluous. Much of the substantive controversy about revisions in the Toxicology Protocol centers on the issues of what are the additions to knowledge gained and the circumstances in which that knowledge does not affect conduct of trials in humans.

Toxicology testing generally is agreed to yield information that might be useful in three areas--estimation of safe starting dose for humans, predictions of organ-specific toxicity, and identification of substances too dangerous to test in humans.

1. Estimation of Safe Starting Dose for Humans

A starting dose is sought that is small enough not to be lethal, but large enough that it or a dose not much larger than it might have some beneficial effect. Since beneficial effects of cytotoxic drugs often occur only with doses that also are toxic, this approach necessitates that the starting dose fall in a rather narrow range -- at, or slightly below, the dose that is mildly toxic. Several studies indicate that toxicology in mice yields information that is reasonably predictive of doses that are tolerated by humans. In 1981 NCI completed the quantitative analysis of a Mouse Lethality/Toxicity Study of 19 drugs representative of the various classes of cytotoxic drugs. For the 18 for which the mouse LD_{10} and human maximum tolerated dose (HMTD) were both determined, the ratio of HMTD to one-tenth the mouse LD_{10} ranged from 1.64 to 103.77, and was less than 16 for 17 drugs. Although these results suggest that the risk of giving humans one-tenth the mouse LD_{10} (on a mg/m^2 basis) might be acceptably small, the latest version of the Toxicology Protocol calls for starting with a still smaller dose if dogs do not tolerate the initial

Table 1

Organ-Specific Toxicity of 25 Toxic Drugs in Humans: Comparison of Observed Predictiveness of Dog Toxicity Results with That Expected by Chance Alone*

	Results in Dog							
	Toxic			Non-Toxic			Total (N=25)	
		Toxic in Humans			Toxic in Humans		Toxic in Humans	
Organ System	No. (A)	Obs.	Exp. (AxC)	No. (B)	Obs	Exp (BxC)	Obs	% (C)
Gastrointestinal	25	23	23.00	0	0	0.00	23	92
Bone Marrow	23	20	20.24	2	2	1.76	22	88
Liver	24	13	12.48	1	0	0.52	13	52
Renal	22	8	8.80	3	2	1.20	10	40
Cardiovascular	13	7	5.20	12	3	4.80	10	40
Neuromuscular	21	6	5.88	4	1	1.12	7	28
Integument	11	3	3.08	14	4	3.92	7	28
Injection Site	13	4	3.12	12	2	2.88	6	24
Respiratory	20	4	4.00	5	1	1.00	5	20
Lymphoid	19	1	0.76	6	0	0.24	1	4
Total	191	89	86.56	59	15	17.44		

* adapted from Rozencweig, Marcel, et al. "Animal Toxicology for Early Clinical Trials with Anti-Cancer Agents." Cancer Clinical Trials, Vol. 4, 21-28, 1981.

dose determined from mouse studies. The trade-offs between increased safety and decreased efficiency that are inherent in the decision to confirm in dogs the starting dose suggested by studies in mice are not easily quantified precisely with experience from only a few drugs.

2. Predictions of Organ-Specific Toxicity

The area of prediction of organ-specific toxicity is more controversial. Most of the controversy hinges on whether the sensitivity or the predictive value of testing in animals is more important in providing information about the organ-specific toxicities that might be expected in humans. The sensitivity of a test represents the proportion of cases of the condition (e.g. toxicity in a particular organ in humans) in which the test was positive. The predictive value of a positive test represents the proportion of instances with a positive test in which the condition actually exists. Guarino, emphasizing the importance of test sensitivity, observed that in tests of 44 cytotoxic drugs that caused human toxicity in 120 drug-organ combinations, toxicity in dogs had been observed in 97 of the same drug-organ combinations -- indicating a sensitivity of 81 percent. He argued that, because dog testing provides a warning about the large majority of toxicities later seen in people, emphasis on qualitative toxicity testing in dogs should be retained. Rozencweig and colleagues, emphasizing the importance of predictive value of tests, compared estimates of the probability that a drug would cause toxicity in humans in a particular organ for drugs that did or did not affect that organ in dogs. In an analysis of 25 of the 44 cytotoxic drugs studied by Guarino, they found that the results of testing in dogs did not differentiate between drugs that would or would not affect a particular organ in humans. Overall, of the 191 drug-organ combinations which in the dog showed toxicity, 89 showed toxicity in humans whereas 86.6 would have been expected by chance alone (Table 1). For example, toxicity of the respiratory tract in humans was seen in four (20 percent) of 20 drugs toxic to the respiratory tract in dogs and in one (20 percent) of five drugs not toxic to dogs. Thus, toxicity of the respiratory tract in dogs was not helpful in predicting the occurrence of that toxicity in humans. Task Force reanalysis of Guarino's results shows that the organ-specific sensitivity of dog testing for those same 25 drugs is 74 percent (43 of 58), which shows that this subset of 25 drugs is not much different from the entire 44 drugs studied by Guarino. In summary, it seems that, in the classes of drugs for which dog and human organ toxicities have been compared, organs commonly affected in humans are also commonly affected in dogs (resulting in high sensitivity); but that for an individual drug, one does not learn from organ toxicity in dogs much about the probability of that given organ being affected in humans (as evidenced by similar rates of organ-specific damage in humans from drugs that do as from those that do not exhibit toxicity of that organ in dogs). This points up the fact that for a test to be useful it is not sufficient for it have high sensitivity. Whether or not organ-specific drug toxicities in mice are predictive of events in humans is a topic of study under the new Toxicology Protocol from which results are expected in two to three years, a target date said by NCI staff to be unaffected by NCI's recent proposal explicitly to state that the mouse toxicity studies were optional.

If organ-specific toxicities in animals were predictive of damage to the same organs in humans, analysis of animal testing should be completed before the stage of human testing in which results of that analysis would affect conduct of the clinical trials, including patient monitoring. The current decision not to require routine submission of histopathology in animals prior to Phase I studies has been justified on several bases: (1) that animal testing is not predictive of results in humans; (2) that all organ systems are closely monitored during Phase I trials so that knowledge of the histopathology, even if it were predictive, would not affect conduct of the human studies; (3) that histopathology has never uncovered a toxic effect not suspected from other studies that would affect the conduct of the trial; and (4) that it is important to speed the introduction of all promising cytotoxic agents into clinical trials.

3. Identification of Substances Too Dangerous to Test in Humans

The third area, the culling out of drugs too dangerous to test in humans, provides a check on the general NCI philosophy that any drug active in animal tumor screening systems should be tested in cancer patients, regardless of toxicity. Ten agents have failed to pass the equivalent of step III in the DN and therefore were not advanced to Phase I trials. Reasons for stopping development of most of these agents were severe, irreversible, or unpredictable toxicity. For example, phleomycin (NSC-61586) caused delayed, irreversible renal damage that could not be predicted, and coralyne sulfoacetate (NSC-154890) caused unmanageable intravascular coagulation and delayed irreversible debilitation. Despite the lack of scientific evidence that such toxicities in animals would be predictive of similar events in humans, the decision not to proceed with Phase I testing is easily understood on humanitarian grounds.

D. Consequences of the New Toxicology Protocol

The success of the new Toxicology Protocol in overcoming the deficiencies of the 1973 version cannot yet be fully assessed. It is not certain that the hoped-for, more rapid development of drugs will occur. For the first two drugs tested under the new Protocol, intervals from starting toxicity testing in animals to deciding to file an IND were seven months and nine months, compared to a median of eight months (a range of five months to 28 months) in the last seven drugs tested under the old Protocol. The intoduction of the requirements for Good Laboratory Practices and the need to expand testing in mice to obtain reliable estimates of LD_{10}, LD_{50} and LD_{90} have lengthened the time necessary for toxicology testing. Dropping the testing of monkeys and the use of intermittent doses in dogs has simplified the work. The former change, however, was made in 1979 somewhat independently of the overall revisions of the Toxicology Protocol, and the crispness of the latter change as originally proposed by NCI in 1979 has been softened by an evolving requirement that dosing be escalated in dogs until frank toxicity is demonstrated. The rationale for the latter change is unclear: various FDA and NCI staff justify it as a way to detect the types of toxicity seen with intermittent or high dosing that might predict organ-specific damage in humans; as an indicator of the need to lower the dose escalation steps in Phase I trials; and as a source of information for a later study of the utility of data from the dog studies in deciding to increase the starting dose in humans suggested by mouse studies. The effect of the changes on the overall cost of toxicology testing has not yet been measured although it has been estimated by NCI staff to average about $100,000 less per drug than with the 1973 Protocol.

A continuing problem with the present version of the new Protocol is the lack of clear decision rules regarding when additional toxicity testing will be required before Phase I studies can proceed. Dr. Crout's July 9, 1981, memorandum states that "in the event of possible marked drug cumulation (as evidenced by a large increase in drug toxicity on the x5 schedule as compared to the x1 schedule) or in the event of possible irreversible injury (as evidenced by mice or dogs failing to recover from sublethal doses), additional toxicology studies directed toward the specific problem would need to be done before evaluation of the drug could begin in humans." The Task Force, however, has seen no evidence that clear decision rules to implement this policy have yet been inserted in the Toxicology Protocol. Furthermore, the failure to require that mice and dogs be observed until toxicity reverses makes it possible that their "fail[ure] to recover from sub-lethal doses" will go undetected.

The Toxicology Protocol also does not specify the requirements for testing of carcinogenicity and teratogenicity. FDA's Oncologic Drugs Advisory Committee endorsed the Toxicology Guidelines Committee statement that this testing should be completed prior to NDA approval. Considering the urgency and importance of using whatever new drugs are demonstrated to have efficacy in cancer patients, it is not certain that this can be accomplished. Surely the problem should be explicitly addressed in the immediate future. Both FDA and NCI staff have indicated their awareness of this problem and the need to develop new methods for testing the chronic toxicities of this class of cytotoxic agents.

E. Management and Evaluation of the New Toxicology Protocol

The animal testing under the Toxicology Protocol is done under contract, the present principal contractor being Batelle Memorial Institute Columbus Laboratories. No estimate of error rates in the primary data has been made, but the contractor has developed a set of procedures for monitoring the performance of subcontractors. A Quality Assurance Officer of the contractor is to visit each subcontractor initially and at least annually to determine that the Toxicology Protocol and standard operating practices are being followed and that data are accurately calculated and reported. For ongoing studies, the site visit will include detailed analysis of the accuracy and completeness of the records of a random sample of (possibly as few as two) animals. The Quality Assurance Officer is to submit a written report to the contractor. If findings suggest the need for corrective action, a copy of the report is to be sent to NCI.

Evaluation of information developed under the Toxicology Protocol occurs at four levels. The subcontractor is required to review accumulating data and report to the toxicology prime contractor, who in turn is responsible to review data weekly. Reports from the contractor are given on request (but at least fortnightly) to and are reviewed by the Toxicology Branch, Developmental Therapeutics Program, NCI. The decision whether or not to proceed with an IND and clinical testing is made by the DN (Step III). The IND in turn is reviewed by FDA's Division of Oncology and Radiopharmaceutical Drug Products, and by FDA's Oncologic Drugs Advisory Committee.

The system for evaluating the scientific strategy of the new Toxicology Protocol has not been formalized, but many parts of it seem clear to NCI staff. A commitment has been made to evaluate the value of the mouse histopathology in predicting human organ-specific toxicity, as suggested by the Toxicology Guidelines Subcommittee of FDA's Oncologic Drugs Advisory Committee. There is continuing interest in assessing the value of dog histopathology and other components of the protocol studies to determine their utility in prediction of human toxicity. NCI plans to evaluate the quantitative predictiveness of the new Protocol by calculating toxicity ratios (predicted safe starting dose/maximum safely tolerated dose in humans) to estimate the margins of safety and the numbers of dose escalations required to reach a clinically effective dose. These evaluations are to be continued as clinical data are accumulated. Interim summaries of findings with the first nine drugs under the new Toxicology Protocol have already been provided to FDA by DCT both by letter and in meetings and to DCT's BSC in their June 1981 meeting.

F. Conclusions

The Toxicology Protocol has been revised through a long, thoughtful, and open process which permitted the consideration and, in some instances, acceptance of dissenting views. The principal aim of the process of revision -- to produce a more streamlined Protocol for pre-clinical toxicity testing that reflects the accumulated knowledge of the utility of that testing -- seems largely to have been accomplished. The major part of the new Protocol appears to have the support of the great majority of the oncology community. The length and openness of the process have led to several problems, however, that have not yet been solved. The many changes that have been suggested and accepted since NCI first proposed the new Toxicology Protocol in 1979 have resulted in there being no single document that all agree is the new Toxicology Protocol. As a result there is considerable misunderstanding among FDA and NCI staff as to the details of the Protocol. As one example, the version of the Toxicology Protocol in the DMF as of December 14, 1981, did not specify how the results of animal testing will be used to determine the initial dose for humans. As a second, some FDA staff have criticized the new Protocol for its failure to include determination of a dose-adverse response curve in dogs, but were not aware of the recent change that provided for escalating doses in dogs until frank toxicity is reached, a reversal of NCI's 1979 position. As a third, the criteria for determining when additional toxicity testing in animals will be required before starting human trials--required by Commissioner Hayes when he approved the new Protocol in October 1981 -- have not yet been formalized or included in the DMF.

The evolutionary character of the new Toxicology Protocol is an expected and desirable quality but the lag in that process lessens the credibility of formal approvals given at earlier stages of its development. FDA's Oncologic Drugs Advisory Committee approved in 1979 a version much different from that now in place or proposed. For example, their Toxicology Guidelines Subcommittee directed that animals that had not yet recovered from the acute effects of toxicity experiments should not be killed, but rather be observed to see whether the toxicity was reversible, whereas, the present version of the Protocol does not permit continuing observation of mice and makes such observation of dogs optional.

Despite these problems, a protocol appears to have been agreed to which, in large part, seems fairly to reflect the state of understanding of the usefulness of preclinical toxicity testing and which accommodates the most persuasive concerns of its earlier critics. Further there is no difference in the manner in which industry or NCI would be treated with regard to this class of drugs; all aspects of the Toxicology Protocol used by NCI sponsorship of INDs could also be used by industry upon request. There is the need now to write down all that has been agreed to and to seek a grand round of approval -- including approval from those who have previously given it. The FDA proposal to publish the Protocol in the Federal Register for general comment is reasonable, and the comments generated will provide additional information and perspectives that may aid the deliberations of the advisory committees.

Recommendations -

1. The value of the dog and mouse as predictors of qualitative toxicity, the value of dose escalations in dog in predicting cumulative toxicity, and the effectiveness of the proposed scheme for selecting a safe and efficient starting dose for humans should be reconsidered repeatedly in light of accumulating experience under the new Toxicology Protocol. A schedule for such reconsiderations should be drafted by NCI, as it would improve the chances that appropriate changes in the Protocol would be made promptly, and would enhance the credibility of this important scientific and medical document.

2. The updated new Toxicology Protocol -- including contingencies for nonrountine testing (such as testing for possible cumulative toxicity and performance of animal histopathology prior to human testing), a description of how the results will be used to calculate the initial dose for humans, and the planned schedule for analysis of accumulating results -- should be assembled and presented to the appropriate FDA and NCI advisory committees for approval.

VI. CLINICAL TRIALS

The decision to initiate clinical testing of a new antineoplastic drug by NCI is one in which NCI and FDA must concur. NCI's DN committee sets the process in motion by deciding that the agent shows sufficient anticancer activity in animal or *in vitro* systems, and the Investigational Drug Branch (IDB) then compiles *all* the information necessary for the submission of an IND to FDA. The information required is detailed in FDA regulations (Title 21 CFR Part 312), and may be summarized as follows: (1) the identity and chemical characteristics of the drug to be tested; (2) the results of preclinical testing of the drug in model systems; (3) the proposed plan for study of the drug in humans; and (4) where and by whom the testing is to be done. The DMF contains some of this information and, to the extent applicable, may be incorporated by reference. FDA staff review the IND submission, and must agree that the drug is sufficiently promising, that the preclinical testing is complete enough, and that the clinical testing protocol is sound before the drug is administered to the first patient. Regulations provide that 30 days' silence on the part of FDA is tacit "approval" of the IND application.

Organization and Management by NCI

How NCI goes about its sponsored investigation of drugs (as well as other treatment modalities, such as surgery and radiation) is set forth in considerable detail in NCI's "Operational Plan and Procedures for Clinical Trials," which has been incorporated as a part of the DMF. The contents of that document are not repeated here, but rather are included by reference to and comment on certain of its features. Although it is the most comprehensive description that NCI has prepared of its methods and procedures for drug testing, neither it nor any other written document covers the system fully; the Task Force has had to ask NCI staff for clarification of many operational details. NCI and FDA staff have various degrees of familiarity with the system, but understanding of its structure and procedures is not uniform, even within NCI. In part, this may be due to the large number of recent changes in key personnel, but it is a situation that should be corrected.

> Recommendation -
>
> NCI should develop and maintain a single, comprehensive, and updated description of its drug testing organization, its procedural requirements, and the responsibilities of investigators. Copies of this document should be made available to all investigators, centers, cooperative groups, and so on, and utilized in an expanded educational effort.

One underlying feature that should be borne in mind throughout is that the investigators and institutions that play a role in cancer drug testing and receive federal financial support are selected from among many applicants through the competitive peer review system.

Phase I Studies

In Phase I studies, new cytotoxic drugs are first given to humans, starting with small doses unlikely to be either effective or toxic and followed with increasing doses until an appropriate level for more extensive testing has been determined. These are performed in only a small number of institutions under close control by IDB. (See Section VII, Investigational New Drug Distribution and Investigators). Each individual protocol for testing a Phase I drug is cleared by the IRB at the performing institution, and then approved by the Chief of IDB, often with advice from NCI's Protocol Review Committee. These actions are reviewed by the Associate Director, Cancer Therapy Evaluation Program (CTEP), and the Director, DCT. Accumulating data, on a case-by-case basis, are sent by investigators to IDB and to the Clinical Trials Monitoring Service (CTMS) every 2 weeks. Progress at each institution is summarized three times yearly as a scientific progress report, and these results are presented to the community of investigators at the Phase I Working Group meetings. This activity culminates in a determination at Decision Network-4 (DN-4, See Figure 1) either that the drug is well enough characterized with respect to dose and toxicity to progress to Phase II, or that toxic reactions are too severe and the drug must be set aside. Ordinarily, in the latter case the IND is closed, although exceptions have occurred in which one or more investigators holds to a belief that some means to alleviate toxicity can be found.

The principal areas of controversy regarding Phase I studies involve informed consent (which is discussed in Section XI, Protection of Human Subjects) and the number of patients given the drug (which is discussed below.)

Phase II Studies

During Phase I, evidence of anticancer activity has been looked for, although eligibility criteria for Phase I studies do not require that the patient's disease be measurable (e.g., a palpable tumor or an x-ray shadow of a tumor). This is a requirement for Phase II studies, in which tumor response is the principal outcome variable being followed. Since cancer is not one disease, but rather more than 100 different tumor types, each having different biologic and biochemical features, Phase II studies may continue for prolonged periods. Not all qualified investigators can agree on the decision to give up on a drug that is not proving effective. Nor can there be absolute agreement on how many cases of a given tumor to test. Statistics yields a rule of thumb that if a drug's true response rate is 20 percent (i.e., that 20 percent of a large series of patients would respond), there is only a 5 percent chance that no response will be noted in any of the first 14. Thus, it is reasonable to stop testing a drug in a given tumor type after 14 consecutive failures. If, however, one or more of the first 14 patients responds, one should increase the sample to at least 25. Such decision rules are, however, only guidelines; they are starting places which must be modified on the basis of other information, such as a chemical relationship between the drug and another of known efficacy or the fact that the drug has already been found to be beneficial in another, possibly biologically related, tumor type.

One recurring criticism of NCI's clinical trials, which appears to the Task Force to have justification in fact, is that too many patients are enrolled in some Phase I and Phase II studies, even though results to date on a given drug have been consistently negative; other Phase II protocols, which might yield useful information, are not being completed in a timely manner. This problem should be relatively easy to rectify by focussing attention on the determination of sample size in clinical trial protocols and enforcing adherence to the approved protocol during its execution.

Recommendations -

1. NCI should require that every protocol include a clear statement of the number of patients to be studied as a condition for approval, and that a proposal to amend that number be approved by the appropriate IRB(s) and NCI committee(s).

2. Each protocol should also show how patient accrual will be monitored as execution of the study begins, and how accrual will be stopped when the approved sample size has been achieved.

3. The quantity of drug that will be required to complete the approved protocol should be estimated at the outset, and the cumulative amount shipped under the protocol number not be allowed to exceed the estimate without an explanation and a check on total patient accrual.

The issue of selecting which and how many drug-tumor combinations to test in Phase II presents a paradox. On one hand, oncologists believe that the failure of a drug to give clinical responses in several tumors does not diminish the probability of response in the next tumor type to be tested. As a result, a panel of six tumor types has been designated as signal tumors against which NCI indicates each cytotoxic drug should be tested, as a minimum, before consideration is given to halting testing of that drug. In fact, it is likely that NCI would agree to an investigator's proposal to test the drug in other tumor types even if the drug had been ineffective in all six panel tumors, and possibly others. On the other side of the paradox, NCI staff indicate that it is difficult to finish testing of the panel tumors for a drug with which early results are not promising. Investigators apparently are reluctant to enroll patients with a given tumor in a study of a drug already shown to be ineffective in several other tumors; they prefer, instead, to try a drug with which there is little prior experience. Resolution of the paradox would have important implications regarding not only strategy for drug development but also the ethics of drug testing since patients should not be asked to participate in, and money should not be spent to conduct, drug trials for which the probability of a clinical response is vanishingly small.

NCI has not formally used accumulating Phase II testing data to attempt to resolve the paradox by determining whether success or failure in one tumor type affects the probability of success in subsequent tumor types; but, at the request of the Task Force, NCI provided data for an independent analysis. Considering the 20 drugs approved as INDs and entered into Phase II trials since 1975, insufficient numbers of panel tumors have been fully tested to permit a clear answer, but some provocative trends are apparent. For example, the eight drugs that showed a 10 or more percent response rate in leukemia were compared with the four that showed less than 10 percent response. Those that showed a 10 or more percent response rate in leukemia were found to be effective in six other tumor-drug combinations, whereas 4.76 would have been expected on the basis of the overall responsiveness of the other tumors tested; in contrast, using leukemia-ineffective drugs, only three effective tumor-drug combinations were seen although 4.23 were expected. The difference does not approach statistical significance, but the trend suggests the potential value of repeated analyses of this sort as additional Phase II study results are accumulated.

In summary, there is at this time no scientifically sound basis for making a decision to abandon further Phase II testing against additional types of cancer when results with a number of common types have proved negative. The fact that drugs exist which favorably affect only one or a few uncommon types of cancer argues against the adoption of any rigid stopping rule; yet, common sense suggests that a drug which has been repeatedly tested with no response observed need not be fully tested on each and every one of the pathologically differentiable types of cancer. As data accumulate from the completion of progressively more Phase II studies, with both the number of drugs and the number of tumors that have been tested continuously increasing, NCI has the opportunity to define patterns of association, if such exist.

Recommendations -

1. NCI should conduct analysis of treatment results at appropriate intervals to define the degree to which the effectiveness of a drug in one tumor affects the probability of effectiveness in another tumor, and the results should be incorporated into the decision process that assigns priorities to Phase II protocols.

2. NCI's IDB should take a position of clearly understood leadership in the execution of the requisite number of Phase II drug tests on varying types of cancer so that initial determination of the possible clinical efficacy of a drug will not be long delayed after the completion of Phase I. This recommendation includes the negotiation of additional clinical testing contracts, if necessary.

Phase II studies are carried out by a larger number of investigators than Phase I, but the number is still small and closely overseen by IDB. Most of these investigators are also funded through contracts, and interim scientific reports are provided twice yearly when all members of the Phase II Working Group meet and share results. Phase II protocols must be reviewed and approved by the IRB at the performing institution and then by the NCI Protocol Review Committee; the Chief of IDB; the Associate Director, CTEP; and the Clinical Director and Director, DCT.

Drugs in late Phase II, which have been shown to induce responses in one or more tumors at an encouraging rate, are distributed as Group B drugs as described in Section II, Cytotoxic Drugs - Background. These late Phase II studies differ from the preceding in three principal characteristics -

1. Since the drug is in Group B, the number of investigators and institutions who gain access to and use it is larger.

2. The drug may be used as part of a combination in an attempt to work out interactions and to design regimens that will be definitively evaluated in a randomized, or otherwise controlled, Phase III study; this is part of a shift of emphasis from testing the individual drug to the treatment of the disease.

3. The initiative in the design of the study is considered to be the prerogative of the investigator, not NCI.

Phase III

If a drug shows signs of efficacy in any Phase II study, and toxicity is not devastating or uncontrollable, it becomes the subject of Phase III investigations. This transition may be simultaneous with, or may follow soon after, NCI's decision to advance the drug to Group B distribution status. It is in Phase III that the pathway for the development of clinical knowledge of antineoplastic drugs diverges most markedly from the accepted routines for the study of other drugs and in which the multiplicity and diversity of the NCI's therapy development and evaluation activities become most evident.

The purpose of Phase III investigations is to establish the place of a new drug in the armamentarium of the clinical therapist. It is not so much to discover whether the drug in isolation is active or not, as (1) to compare it with alternative active drugs and other modalities of treatment; and (2) to establish in which types of cancer or in which stages of disease a regimen containing the new drug is superior to older, accepted ones. Since few of the currently preferred regimens for the drug treatment of cancer use a single agent, a common design for a Phase III clinical trial involves the comparison of a multidrug or multimodality approach that includes the new drug with the multidrug regimen that is deemed to be the most successful of those already in practical use. It is evident that the scientific focus of Phase III research has shifted from the drug to the disease.

At the same time, the principal responsibility for support of the clinical research shifts from IDB to the Clinical Investigations Branch (CIB), and a large share of the intellectual responsibility for the design and execution of research shifts from NCI to the academic and medical community of clinical oncology. The research may be funded by either contracts or grants (many of which are now being converted to cooperative agreements), but is given peer review in either case. In each area, requests for funding exceed NCI's capacity to pay so that the selection process is highly competitive. The great majority of the performers of these Phase III clinical studies are at cancer centers and hospitals associated with the university hospitals or medical schools.

Phase III studies require a larger number of patients than do Phase II trials since one is seeking to demonstrate a possibly small difference between the efficacy of a new regimen and that of the best existing one. The Phase II question - does the drug have some effect or none? - is more direct. Recruiting the requisite number of similar cancer cases is often beyond the capability of one institution, even a big city cancer center, so that it has been necessary to establish cooperative groups that can involve more than one institution in a single study protocol. Some of these groups are oriented toward particular tumor types, such as the brain tumors or gastrointestinal tumors, while others are affiliations of institutions with a geographic focus, such as Southwest Oncology Group (SWOG) or Eastern Cooperative Oncology Group (ECOG). (See Section VII, Investigational New Drug Distribution and Investigators.)

When a drug becomes available for Phase III studies, NCI makes the information known to all of these groups. Plans for specific studies -- protocols -- are then originated by research oncologists within those groups who have the requisite knowledge and interest and in whose facilities a sufficient number of patients appears for treatment. An important determinant of the availability of a given investigator or institution for a new study is the status of studies currently underway; there may be an important trial nearing completion that will limit the number of cases that could be considered for the new protocol. Once a protocol has been drafted and agreed upon by enough investigators within a group so that it might be feasible to execute it, it must be reviewed and approved by multiple IRBs, one at each of the institutions that might cooperate. It must then be forwarded to NCI and reviewed and approved by the Protocol Review Committee; the Chief, CIB; the Associate Director, CTEP; and the Clinical Director and Director, DCT. Even though the research is to be funded under a grant, which in another field would relieve an NIH Institute of the responsibility of reviewing the detailed protocol, the specific requirement for NCI review has been a provision of the center and cooperative group grants for many years. With the conversion of many of these grants to cooperative agreements, this active participation by NCI is made more formal.

When Phase III studies are begun, the focus of NCI has shifted to the disease, while FDA remains, by law, concerned primarily with the drug. Most research oncologists are convinced that they will obtain the best therapeutic results with drug combinations, so that the design at this stage of a single drug study that will clearly illustrate the value of a drug may appear unethical. Even the superficially attractive idea of testing new drug X in combination with accepted drugs, Q, R, and S against the QRS combination alone is usually not acceptable. QRS may already be at the margin of acceptable toxicity and will probably be pushed across the border by the simple addition of X unless one or more QRS drugs is omitted or the dosage reduced. NCI appears to some FDA staff to be unable or unwilling to carry out a scientifically satisfactory Phase III study; yet, it is clear from the record of research over the past decade that a number of drugs have gradually found secure places in the practice of clinical oncology and that overall survival of cancer patients has improved. Admittedly, this is much more in the drug-treatable cancers, such a lymphoma and leukemia, which were formerly always and quickly fatal, than in the solid epithelial neoplasms, which remain intractable if they cannot be removed surgically.

With the existence of over 100 distinct types of cancer, and with the multiplicity of possible therapeutic regimens that may be tested using drugs in combinations or with other treatment modalities such as X-ray, it is apparent that investigational use of a new drug in Phase III studies may proceed for many years. Even after a drug is officially approved through an NDA for one or more specific indications, it is likely to be the continuing subject of studies to determine its efficacy in treating different, perhaps less common, types of cancer, and/or its potential synergistic effects in novel combinations. The fact that investigations of this sort are viewed by NCI as central to its mission lessens the Institute's interest in seeing that drugs receive NDA approval promptly. NCI has traditionally believed that (1) the pharmaceutical industry should assume the responsibility for obtaining NDA approval and for marketing the drugs that appear to have established utility, and (2) that the Institute's resources should be husbanded for the support of research that will further basic understanding of the principles of cancer treatment and further extend the range of potentially therapeutic compounds about which some information has been gathered.

Industrial concerns, however, have been reluctant to invest effort and funds to bring anticancer drugs to market, principally because their profit potential has remained weak. Though cancer is an enormous health problem in America and one of the leading causes of death, the number of patients for whom drug treatment is indicated at any point in time is small compared with the number for whom analgesics or anti-hypertensive medications, for example, might be prescribed. The fact that no one drug is best for all types of cancer further limits the market potential for any individual product. Finally, it is clear that none of the drugs now available is highly efficacious, and that NCI is continuing an intensive search for better methods of treatment. Therefore, any drug marketed today could be quickly superseded by a superior therapy in the near future, possibly long before a company that had decided to market it had recouped its investment in obtaining approval and in promotion. All these considerations make anticancer drugs typical members of the "orphan drug" category -- drugs that are needed by and important to a limited population of patients, but whose market potential is too low to attract investment by industry.

The establishment of NCI's Group C drug category represents an attempt to resolve this dilemma by institutionalizing the so-called "compassionate IND" in the anticancer field. When NCI staff and the oncology community feel that the evidence is strong that a particular drug has a beneficial effect in one or more types of cancer but no one is prepared to submit an NDA, NCI can propose to FDA that the drug be made available for wide distribution in Group C (see Section VII, Investigational New Drug Distribution and Investigators). The summary evidence is reviewed by the FDA's Oncologic Drugs Advisory Committee,* but FDA does not inspect the raw data in the detailed fashion that it requires for the approval of an NDA. In effect, the investigators are taken at their word with respect to the veracity of the individual patient records that have been submitted for analysis. The Committee reviews only the logic of the experimental design and the appropriateness of the data collection and analytic procedures reported; it judges whether the result is sufficiently convincing to justify the distribution of the drug primarily for treatment as opposed to primarily for research.

When a drug has been moved into Group C, it is supplied at no charge by NCI to physicians, clinics, and hospitals that are registered through the submission of form FD 1573, and that have an IRB to review individual proposals for the use of Group C drugs. The drugs cannot be bought through pharmacies, nor prescribed by physicians who are not registered. Purchasing and distributing Group C drugs is a major expense for NCI and one which yields only a modicum of scientific information through the reporting of adverse reactions. Treatment outcomes are not systematically reported and studied when Group C drugs are used for primarily therapeutic purposes, and there would be no valid control group for comparison if such results were to be obtained. Thus, NCI's provision of drugs through Group C is primarily a response to pressure to make the fruits of research available to patients in need, and not a research effort itself.

---

*The FDA Oncologic Drugs Advisory Committee was established in October 1973. It consists of 11 members appointed by the Commissioner of Foods and Drugs for overlapping terms of 4 years. Members are selected from experts in oncology, statistics, and related medical disciplines. The committee reviews and evaluates available data concerning the safety and effectiveness of marketed and investigational drug products for use in the treatment of cancer and makes appropriate recommendations to the Commissioner of Food and Drugs. Meetings are held four times a year as called by the Director, BD, FDA.

The very existence of Group C, however, is a disincentive to a drug firm that might consider sponsoring an NDA for an anticancer drug. Whereas the NDA and marketing effort may be too financially risky to be attractive, the company has the immediate opportunity to make a limited amount of money selling the drug to NCI without further investment of its own resources. These many factors, scientific and economic, underlie the notable tendency of anticancer drugs to remain for long periods in investigational status under NCI sponsorship, even though practicing oncologists have accepted the evidence for their efficacy and they have become standard methods for the treatment of cancer patients in the specialized centers.

Since NCI reviews all protocols for the investigational use of sponsored drugs, the Institute has the information required to maintain a complete inventory of its ongoing research. For years, NCI has published an annual compilation of clinical protocol summaries in which the critical design elements of each study are summarized. These summaries are indexed by performer and by drug(s) and can be consulted in either the published form or through MEDLARS. The computerized data base of the National Library of Medicine is revised quarterly. Thus, not only NCI staff, but also investigators in the field have easy access to a listing of all ongoing studies and can avoid the wasted effort of submitting or reviewing plans which are too redundant to be of value. This system, however, cannot be used to track the progress of ongoing studies.

The findings in Phase III clinical trials are reported in preliminary form at the investigators' meetings of the cooperative groups, which also subserve the functions assigned to Data and Safety Monitoring Committees for clinical trials in many other fields. The main reason for having separate data monitoring committees in other fields -- the wish to maintain a double-blind design in which the investigators do not know which patient is on which treatment -- does not usually occur in cancer trials. In this area, it is usually difficult and sometimes impossible to impose and maintain a blind status because of the obvious side-effects of most of the drugs.

As results become more mature, they may be presented at the open meetings of medical and scientific societies and ultimately published in the refereed medical literature. None of these media, except the reports to the Data and Safety Monitoring Committees, includes the results of treatment on a case-by-case basis; instead, they focus on summaries and results of statistical analyses, preserving the confidentiality of individual medical records. This is analogous to the process by which other advances in nonpharmacologic medical treatment are made known to, and accepted by, the profession.

NCI Review and Advisory Committees and Groups

An elaborate network of committees oversees the NCI drug development and testing program, examining its progress in terms of both advances in antineoplastic drugs and in integration of chemotherapy with other modes of treatment such as surgery and radiation. An assessment of the overall progress of the National Cancer Program is provided by the President's Cancer Panel, a chartered body of three members, at least two of whom are distinguished scientists or physicians. This Panel meets at least four times a year to monitor the development and execution of the program, evaluate its efficacy, suggest improvements, and submit periodic progress reports to the President.

The National Cancer Advisory Board (NCAB), successor to the National Cancer Advisory Council, which was established by statue in 1937, is composed of 18 members appointed by the President and eight nonvoting, ex officio members. The appointed members include scientists and physicians outstanding in the study, diagnosis, and treatment of cancer, as well as representatives of the general public. Among the nonvoting members are the Secretary, HHS; Director of the Office of Science and Technology Policy; Director, NIH; Commissioner of Food and Drugs; and Chairman, Consumer Product Safety Commission. This Board meets at least four times a year to advise and assist the Director, NCI, with respect to the program priorities and the funding of the cancer program, and to conduct a second-level review of proposals for cancer research grants. The Board also oversees the contract reviews done by the Board of Scientific Counselors (BSC).

The Director, NCI, in 1974 established BSC, DCT, which succeeded the Chemotherapy Advisory Committee. This group consists of 15 members selected from authorities knowledgeable in the fields of cancer treatment, biology, chemistry, pharmacology, immunology, biochemistry, radiobiology, and molecular biology. They meet three times a year to provide advice to the Directors, NCI, and DCT, concerning the progress and direction of DCT. The group also reviews, in concept, proposed contracts and applications for grants. This group conducts periodic and detailed reviews of the DCT Intramural Program, examining each laboratory or branch every 4 to 5 years.

The Cancer Special Program Advisory Committee consists of 16 members appointed by the Director, NCI, and selected from authorities knowledgeable in the field of carcinogenesis, pharmacology, immunology, tumor biology, radiobiology, and viral oncology. This Committee meets three times a year to review the scientific and technical merit of grant-supported programs of the major cancer research institutions. It makes recommendations to the Director, NCI, and the NCAB concerning the productivity, scientific leadership, quality of personnel, future potential, and management capabilities of each applicant institution.

The Cancer Clinical Investigation Review Committee consists of 24 members, appointed by the Director, NCI. Members have training and experience in the fields of medical oncology, surgery, radiation therapy, pediatrics, gynecologic oncology, pathology, and biostatistics. This group, which meets three times a year, advises the Director, NCI, and the Director, Division of Extramural Activities, concerning the scientific merit of applications from cooperative groups for research grants or cooperative agreements to support cooperative clinical trials and related areas of cancer research.

The Clinical Cancer Program Project and Cancer Center Support Review Committee consist of 40 members appointed by the Director, NCI. Members are selected from authorities knowledgeable in the fields of cancer center administration, medical, surgical, and pediatric oncology, radiotherapy, viral oncology, immunology, biochemistry, epidemiology and biostatistics, chemotherapeutic agents, cell regulation and metabolism, and laboratory animal medicine. The Committee operates as two 20-member subcommittees - the Clinical Cancer Program Project Review Subcommittee and the Cancer Center Support Review Subcommittee. The Committee meets three times a year to advise the Director, NCI, and the Director, Division of Cancer Research Resources and Centers, concerning applications for program projects grants and for cancer center core-support grants.

The Clinical Trials Committee consists of 25 members appointed by the Director, NCI. Members are selected from authorities with broad experience in the fields of clinical immunology, clinical pharmacology, clinical radiotherapy, and surgery. This group meets four times a year and provides advice to the Director, NCI, the Director, Division of Extramural Activities, and the Director, DCT, concerning the scientific merit of contract proposals for clinical trials of experimental treatments for cancer.

In addition to these committees, there are 14 other chartered advisory committees assessing various aspects of the National Cancer Program. Although these do not directly review the drug development activities of investigators, their activities have an obvious impact on the chemotherapy program's priorities and resources. For example, committees such as the Bladder and Prostatic Cancer Review Committee, the Breast Cancer Task Force Committee, and the Large Bowel and Pancreatic Cancer Review Committee play an important role in the testing of those drugs which appear to show promise in the treatment of these types of tumors.

The Clinical Oncology Review Committee is a group of DCT senior staff, chaired by the Chief, CIB, which reviews proposals for new resource contracts and recompetition of resource contracts. The Committee also performs annual reviews of all incrementally funded clinical research and resource contracts. They are assisted in these reviews by outside consultants representing a wide variety of relevant disciplines.

Many of the critical decisions about the development and testing of an anticancer drug are made by internal committees whose members are NCI staff or clinical investigators. Before clinical testing, compounds have been reviewed by the Prescreen Subcommittee, a working group of seven biological, chemical, and pharmacological scientists in the Developmental Therapeutics Program (DTP). This working group, which meets every other week, decides whether a drug should be tested in the animal tumor panel and whether special testing is indicated. Their recommendations are provided to the Drug Evaluation Committee, a group of staff scientists from both preclinical and clinical programs which examines each compound's activity in the tumor panel or other test systems and assesses its chemical and biologic potential. If warranted, data about the candidate compound are presented to the Pre-DN Committee, comprised of DCT staff members who meet whenever necessary to consider issues such as the feasibility of obtaining sufficient quantities of the drug for further testing and the solubility and stability characteristics which affect the possibility of clinical testing. Recommendations of this Committee enable the Associate Director, DTP, to decide whether or not to present the compound to the Decision Network Committee (DNC).

The DNC is composed of 25 senior NCI staff scientists from all relevant programs within DCT and is chaired by the Associate Director, CTEP. Other key individuals outside the program, including clinicians and FDA staff, are invited to meetings of the DN, as are the "advocates" of the drug in question. The Committee meets about every 2 months and provides advice to the Director, DCT, concerning whether or not to proceed with the testing required to submit an IND to FDA. The DNC continues to be responsible for evaluating the drug as it passes through the various stages of clinical testing, including decisions such as the maximally tolerated dose and an acceptable schedule of administration for a drug in Phase I testing and its suitability for Phase II testing.

The Operating Committee, a staff group chaired by the Deputy Director, DCT, expedites the development of the drug through preclinical testing by assuring that adequate resources are made available and experimental and production deadlines are met. When a drug has been approved for clinical testing, a Drug Monitor Team is organized, composed of the Chief, IDB, and an IDB staff scientist. This team is responsible for directing and assessing the course of the drug testing efforts, including review of protocols, analysis of information on drug studies, and preparation of annual reports to FDA.

The Phase I Working Group is composed of principal investigators (PI) and other key personnel of Phase I contracts, chiefs of the clinical branches of DCT, the chairman of the New Agents Committee of each of the cooperative groups, and other investigators approved by the Associate Drector, CTEP. This group meets three times a year to share information about the results of current and completed Phase I tests, as well as issues related to the methodology of drug trials. FDA staff are invited to these meetings, and the minutes are distributed to all attendees, each PI in the Working Group, and FDA. Meetings of all investigators performing single agent Phase II studies are held twice a year to review progress and consider the need for further testing. Minutes of these meetings are distributed in a similar manner.

A Protocol Review Committee (PRC), composed of CTEP staff, examines each protocol, together with the informed consent forms and the IRB approval, for the clinical studies conducted by contractors, by cooperative groups and occasionally by cancer centers. This protocol review includes consideration of investigations of all forms of cancer therapy singly and in combination, including surgical, radiation, and biologic modalities as well as drug therapy. Protocols, often prepared in consultation with IDB staff, are reviewed by at least two staff members, usually one from the IDB and one from CIB. These written reviews are discussed at the weekly meeting of the PRC; recommendations for approval are considered by the Branch Chief, CTEP; the Associate Director, CTEP; and the Director, DCT. Protocols which the Committee decides to reject, or those needing revision, are returned to the investigator with the review; protocols approved by the Director, DCT, are added to FDA's IND file, and the approval provides the authorization for ordering an investigational drug from NCI. This Committee and the staff members receiving its recommendations are responsible for ensuring that protocols are not unnecessarily duplicative, that the number of patients to be tested is sufficient but not excessive, and that the set of protocols examining a given drug is sufficient to permit a decision to advance or withdraw the agent.

An elaborate network of chartered advisory groups oversees the drug development efforts of NCI, but most of the critical operating decisions are made by CTEP staff members and clinical investigators. Reports of the meetings of these "inhouse" committees are widely distributed, but they do not include enough information about the decision-making procedures used to permit independent judgment of the soundness of the decisions made. The obscurity of the decision-making process may lead to concern among those not involved in those decisions. Accountability to other groups or agencies or to the public is greatly facilitated by decision rules and explicit criteria, but expert groups often find that such rules are hard to construct and explain, and that they may also restrict the introduction and free discussion of significant information and opinions.

Recommendation -

NCI should conduct a systematic analysis of the timeliness and appropriateness of the key decisions made by staff review groups such as the Protocol Review and DN Committees.

The purpose of this retrospective review would be to assist in the formulation and testing of more explicit decision rules and criteria. The study would search for any patterns and possible sources of errors and omissions in the information available to the decision makers as well as any apparent biases or inconsistencies in the decisions reached. This study should provide evidence to confirm or refute the impression that decisions are arrived at in an arbitrary or capricious manner, or charges that NCI staff are reluctant to challenge the activities of prestigious investigators. It should also lead to better specification of the information needed at each point in the decision process.

In view of the central role occupied by IDB and CIB in anticancer drug develoment, the Task Force believes that an annual overview of the work of these branches should be presented to an advisory committee composed of reviewers who are not NCI staff. This review should include a presentation of IDB and CIB policies, practices, and procedures in such areas as clinical trials monitoring, patient accrual, informed consent form review, drug distribution system, ADRs, interface with FDA, and relationships of IDB and CIB to the total DCT program. The BSC, DCT, could serve as the appropriate review committee. An annual report to the Directors of DCT and NCI would reflect oversight activities on the progress, difficulties, and direction of these branches.

NCI staff have proposed developing a computerized Cancer Therapy Evaluation Program Information System (CTEP-IS) to provide scientific and adminitrative information on treatment modalities, diseases, protocols, and investigator teams. The system would abstract information from protocols and status reports reviewed by the various CTEP branches and provide cross references to existing data about drugs and investigators. The system would produce periodic reports on such topics as (1) administrative status of investigational drugs; (2) administrative status of all protocols in the review process; (3) background information to assist in protocol reviews, such as related ongoing studies and the impact of the protocol on drug inventories and by the treatment modality, specific disease, phase of the study, and investigator drug use rates; (4) objectives and results of ongoing studies, and (5) delinquent reports.

The proposed information system could compensate for the information deficits which result from the decentralized innovative investigator-initiated part of the NCI-supported research program and might contribute meaningfully to the interim scientific program analyses and program management decisions.

Monitoring of Clinical Trials by NCI

The early years of NCI's anticancer drug development program were characterized by reliance on the peer review system on the assumption that selection of scientifically meritorious applications and proposals would ensure the acquisition of reliable results. As the chemotherapy program developed, the need for more systematic monitoring -- comprising both data verification and interim analysis -- of clinical trials of these drugs became apparent, and detailed procedures for selecting investigators and reviewing research protocols were described in NCI's document, "Operational Plan and Procedures for Clinical Trials." NCI recognized, however, that even closer surveillance was required for Phases I and II because of the increasing reliance on monitoring of clinical studies for determining toxicity and because animal testing was found not to predict organ-specific toxicity in humans. They also noted that FDA's proposed "Sponsor-Monitor" regulations would apply directly to NCI's role as an IND sponsor. In 1979, therefore, NCI decided to augment its peer review activities with a formal, contract-supported system designed to be at least equivalent to the methods used for data verification by industry and to provide data for interim analysis by NCI staff.

Mathtech, Inc., was awarded a $1.6 million, 3 year contract in October 1979 to establish and test a monitoring service for clinical trials of investigational new agents. The contract calls for the establishment of a central data management resource and a monitoring activity capable of meeting proposed FDA regulatory requirements and providing status reports on each protocol under study. Mathtech receives information from protocol abstracts and patient data records ("flow sheets") submitted by each investigator every 2 weeks. The stated goals of CTMS, as it is presently functioning, are (1) to ensure the accuracy of data collected in early clinical trials; (2) to ensure compliance with regulations for the protection of human subjects; and (3) to ensure that NCI can comply with the proposed FDA requirements for an IND sponsor regarding drug distribution, adherence to research protocols, and reporting of ADRs. Mathtech also has a program of site visits and data audits by physicians and auditors provided by subcontract with G. H. Besselaar Associates.

The computerized system produces two major reports, distributed monthly to investigators and to NCI. The first is a clinical data report which includes demographic, diagnostic, and prior therapy information, as well as laboratory results, physician notes, and an assessment of each course of current therapy. Data are reported for each patient and are summarized by accruals, incidence of toxicity, and distribution of extreme values of abnormal laboratory test results stratified by regimen and dose level. Study summaries for all trials of the same drug are also consolidated in a program summary. The second report is concerned with administrative and management information. The same procotol abstracts and flow sheets are used to examine investigator performance in terms of ineligible or unevaluable patients, courses of treatment completed, and missing data identified by patient and by course. Summary tabulations include number of ineligible patients and number lost to follow-up (e.g., early deaths, refusals), as well as number of unevaluable courses, number not in accordance with protocol, and compliance with the schedule for laboratory tests. Delays in reporting are also noted; a program summary report describes for each institution the percent of patient eligibility, evaluability, compliance, and timeliness.

Site visits are carried out at least annually at each assigned site by physicans on contract. The purpose of these visits is to examine medical data to assess compliance with protocols, informed consent procedures, and federal regulations.

Paramedical personnel visit each site more frequently to follow up on missing data items or to check any which appear to be outliers. Site visits are conducted with 7 working days' notice. In addition to a structured discussion with the PI, using a checklist based on FDA and NCI regulations and procedures, the monitors verify data through careful review of five - 10 randomly selected patient records, checking x-ray, laboratory, or autopsy reports against the flow sheets submitted to Mathtech. They examine the drug security and pharmacy record-keeping system, and they examine the progress of the studies in terms of patient accrual and evaluability. Detailed discussions with the data managers of each site are also conducted. CTMS is now responsible for monitoring 67 protocols from 18 institutions, including all 10 contractors doing Phase I studies. Data concerning 2,400 courses of treatment in 1,200 patients have been accumulated, and data verification visits have been carried out at each assigned site. In addition to receiving routine reports, NCI personnel have been provided with computer terminals in their offices to permit direct questioning of the system.

A number of apparent discrepancies in the management of clinical trials have been observed; these have been called to the attention of NCI staff and PIs by CTMS. Problems include delays in submitting reports after completion of the treatment course, notable differences between sites in percentages of patients judged eligible for the study protocol and percentages of courses completed and evaluable, and discrepancies between laboratory tests stipulated in the study protocol and tests actually performed.

The CTMS Monitor's Report dated September 30, 1981, was available to the Task Force; it summarizes clinical and administrative data from 56 protocols and their PIs' institutions. Average days delay in submitting reports of completed courses of treatment ranged from 24 to 218 days -- 19 investigators were found to have an average delay of more than 100 days. The reports of 42 protocols contained sufficient information to judge patient eligibility -- 10 investigators were found to have met eligibility criteria in less than 75 percent of the patients they studied. Thirteen investigators were noted to have less than 75 percent of their reported cases evaluable (judged sufficient to contribute to greater understanding of the regimen under study). Seventeen investigators completed less than 75 percent of the treatment courses in strict conformance to the protocol with respect to drug adminitration and follow-up interval. Of the 42 protocols, 38 failed to perform 75 percent or more of the laboratory tests stipulated in the protocol.

NCI and the contractor-monitors hold that many of these problems are due to errors in transcribing data, differences in interpreting criteria for patient eligibility, or loss of patients to follow-up. NCI is using the evidence of these problems as educational tools to improve the performance of clincial trials. Investigators and data managers are being informed of the importance of limiting the number of "ineligible" and "unevaluable" patients in their studies, and NCI staff state they are now seeing improvements in the protocols submitted. Since the report of only 1 month's activities was available to the Task Force, it was not possible to confirm this impression. The monitoring contract is still considered a pilot study, and NCI staff feel it has not been operating long enough to evaluate fully its effectiveness. They believe, however, that the system is succeeding in providing data verification with the desired accuracy. They have recently proposed a plan to refine the monitoring system and, as personnel and financial resources permit, expand it to include all Phase II contracts. They have also proposed to establish a Clinical Trials Monitoring Section within the IDB to use the system reports for improving management practices.

Recommendations -

1. IDB should develop procedures for prompt review of the clinical and administrative data problems and findings of CTMS, for implementing corrective action with investigators, institutions, or cancer cooperative groups and for monitoring of the effects of such action upon the performance of the clinical trials.

2. NCI should establish a clinical trials management activity promptly, to add management oversight and enforcement capabilities to the current monitoring effort. This management group should be given responsibility for ensuring that researchers using investigational drugs under NCI sponsorship comply with approved study protocols, distribution policies, and ADR reporting procedures, as well as the requirements for annual reports, informed consent, and good laboratory practices. The activity can provide the information needed by NCI and its advisory committees to evaluate the success of the current research strategy and to compare it with modified or alternate approaches.

3. NCI should examine the extent to which the clinical, laboratory, and pharmaceutical record systems can be linked and reconciled (through standardized records or even through computer coupling) with the drug distribution management system and the clinical trials information system. This would enhance NCI capability to facilitate the tabulation and analysis of data to support a later NDA; and to develop more systematic and efficient investigative and auditing practices, more effective management, and more complete and timely reporting.

CTMS has been modeled on the procedures used by the drug industry to oversee field trials of new products and to ensure the collection of data that will be acceptable to FDA in an NDA. Industry uses systems of this type throughout the process of drug testing, including Phase III trials. The proposed FDA regulations on responsibilities of sponsors of INDs, if promulgated as final, would presumably require NCI to extend CTMS or some equivalent monitoring system throughout its complex drug testing system. This would occur even though many of the investigators are grantees and, therefore, are presumably being assisted by, but are not agents of, NCI. NCI regards CTMS as experimental and believes that the need for its continuation should be evaluated after it has functioned for an appropriate period of time. Some members of the Task Force agree, while others believe that such on-site data verification and compliance monitoring are already clearly needed in at least Phases I and II studies performed under NCI's INDs. The Task Force members all agree that if the results of the evaluation of CTMS reveal widespread substantive deficiencies, not only should attempts be made by IDB to correct these deficienies but also serious consideration should be given to examining the quality of data in other NCI-sponsored clinical drug testing.

Another possibility that some Task Force members believe worthy of consideration is for NCI to reduce markedly the extent to which it acts as IND sponsor to Phase III studies, and limit the coverage of its own IND efforts to Phase I, early Phase II, and NDA-directed Phase III studies, as is described in Section VIII, NCI Investigator-Sponsor Roles: An Alternative.

FDA Monitoring of NCI INDs

After an IND has been "approved," FDA scientific staff track the progress of drug testing through two formal mechanisms. An annual progress report is required to keep an IND active. These reports do not normally contain detailed medical data on a case-by-case basis. The other formal mechanism is the required prompt reporting to FDA of serious or alarming reactions. This second mechanism is not precisely defined, since the interpretation of the words "prompt," and "alarming" permit considerable latitude of judgment. FDA's role in the second mechanism is passive. FDA can be aware of the overdue annual report, but only rarely will learn of an ADR if formal notification has not occurred. In addition, there are a number of other channels of communication that provide information to FDA on the progress of NCI's IND research. FDA staff may attend meetings at which results of current research are presented. Written manuscripts or summary minutes of such presentations may be forwarded to FDA as they become available. If accumulating information leads to the design and approval of new protocols using an investigational drug, these are forwarded to FDA for inclusion in the active IND file.

An active IND can be terminated by FDA if its medical staff believe that information provided in an annual report or an ADR suggests that the risk to subjects is unduly great. The sponsor of the IND can terminate the research at any time and has only to notify FDA that it is doing so; no permission from FDA is required for stopping. The usual reason for terminating an IND is that the scientific questions originally posed either have been answered or found unanswerable. If the answers on a new drug are favorable, the next step is ordinarily the preparation of an NDA. If they are not, the drug is abandoned. In rare cases, an IND sponsor may determine that the risks of continuation are too great, even though the question originally posed remains unanswered.

Thus, the principal foci of FDA's role in the approval of a new drug are two -- the IND decision, after which clinical research is initiated, and the NDA decision, which leads to broad distribution of the drug through marketing and its availability to any practitioner licensed to sign a prescription. There are no major intermediate check points, although FDA's mandate includes continual oversight of the progress of clinical investigations. In the realm of antineoplastic drugs, the governance of most that transpires between the IND approval and the NDA (or the decision to put the drug in Group C) is the responsibility of NCI, which has the dual

Figure 4

MONITORING OF NCI CLINICAL INVESTIGATIONS OF CYTOTOXIC DRUGS

		MONITORING BY NCI		MONITORING BY FDA			
				VIA NCI		DIRECTLY	
		(A) Data Verification	(B) Scientific Program Interim Analysis	(C) Data Verification	(D) Scientific Program Interim Analysis	(E) Data Verification	(F) Scientific Program Interim Analysis
Group A Drugs*	Phase I Trials	CTMS**	CTMS reports; Phase I Working Group; IDB staff analyses	None***	NCI annual reports; Protocol review; Working Group Minutes	None°	None*
Group B Drugs*	Early Phase II Trials	CTMS	CTMS reports; New Drug Liaison Phase II Working Group; IDB and CIB staff analyses	None***	NCI annual reports; Protocol review; Working Group minutes	None°	None
	Late Phase II Trials	None					
	Phase III Trials	ECOG°°	Extensive NCI investigator group meetings	None	NCI annual reports; Protocol review; Cooperative Group minutes	None°	None

* For relationship of A, B, and C Group drugs to Phases I, II, III, see Section II, Cytotoxic Drugs -- Background
** CTMS (Clinical Trials Monitoring Service)
*** Considering giving CTMS information to FDA
° Except for infrequent "for cause" inspections
°° Data verification done by Eastern Cooperative Oncology Group of its own investigations.

role of sponsor with respect to FDA regulations and provider of fiscal and research resources to the community of scientists attempting to find better ways to treat cancer.

A major concern has been the extent to which FDA monitors the NCI INDs as compared with the degree to which it monitors those of industry. The Task Force perceives that some differences exist but feels that more important is whether those differences are appropriate. Figure 4 summarizes the complex nature of the monitoring by NCI and by FDA of the cytotoxic drug program components. Monitoring is separated into two components -- data verification at the bedside or laboratory bench for accuracy and completeness, and scientific program interim analysis of accumulating results of clinical trials. Monitoring by NCI is shown in columns A and B, Figure 4. CTMS, a contractual effort, provides to NCI for its Phase I and early Phase II trials data verification and summary reports which NCI uses in interim analysis of results. Data verification in Phase III is accomplished by one cooperative group (ECOG) for its own trials. NCI interim analysis of clinical trial results for Phases I, II, and III is based on information in CTMS reports; Phase I/II Working Group meetings and reports; New Drug Liaision Group meetings and reports; extensive NCI investigator group meetings; and IDB and CIB staff analyses.

Monitoring by FDA done via NCI is shown in columns C and D of Figure 4, and that done directly by FDA is shown in columns E and F. FDA engages in little data verification of the NCI cytotoxic drug program, either directly or via NCI; infrequent "for cause" field inspections expose some data to FDA staff. CTMS information is available to FDA. This contrasts with the considerable data verification effort of FDA directed toward industry generally occurring through "routine" inspections of investigators' data. However, because of the inspection program surveillance strategy which gives cytotoxic drug IND studies low priority, industry is treated the same as is NCI regarding data verification for this class of drugs.

Recommendation -

> BD should include all of the NCI-sponsored drug investigators within their selection procedures of investigators and institutions for review on a routine basis. To the extent possible, FDA should utilize the results of NCI monitoring to minimize duplication and should utilize FDA inspectors in the regions to conduct the monitoring as is done for other drug monitoring.

FDA oversees NCI's interim analysis processes via review of NCI's submitted annual reports, clinical protocols, minutes of working groups, and cooperative study groups (Figure 4, column D); FDA does not directly perform interim analysis of cytotoxic drug clinical trial results (Figure 4, column F). There has not been any evidence presented that FDA's overview of the NCI interim analysis process is less than that for industry's cytotoxic drug efforts; indeed, the extra communication channels established between NCI and FDA probably give FDA opportunity for greater oversight of NCI than of industry cytotoxic drug interim analyses.

Figure 4 also reflects the monitoring associated with Groups A and B drugs. Monitoring of A and B drugs is a mixture of that given to Phases I, II, and III (see Section VII, Investigational New Drugs and Investigators).

The decision to move a drug into Group C is based on a review of the preceding studies which have been monitored as described previously. The use of a drug in Group C is monitored only to the extent that ADRs are reported.

Comprehensive interim analysis of cytotoxic drug experience is needed. NCI performs interim analysis on the cytotoxic drug experience gained under NCI-sponsored INDs, and FDA has oversight of that analysis. FDA does not, however, engage in comprehensive interim analyses of all cytotoxic drug IND experience -- that of NCI plus that of industry plus that of other individual physicians and medical institutions with their own INDs.

Investigator Responsibilities

On August 8, 1978, the FDA published in the Federal Register proposed regulations detailing "Obligations of Clinical Investigators of Regulated Articles" (Vol. 43, No. 153). These are presently still "proposed." The Task Force believes these should be viewed as reasonable guidelines for investigators.

A key distinction is between the sponsor who initiates the project and the investigator who actually conducts the study and directly administers the drug to the subject. The hybrid category of sponsor-investigator refers to an individual who both initiates and actually conducts a clinical investigation. While less used in oncologic drug investigation, sponsor-investigator research represents almost half of all active INDs in BD.

A written protocol defines the research objectives and outlines the research plan for a clinical study. A clinical investigaton must be conducted in accordance with the protocol. An investigator must obtain prior approval from the IND sponsor for any significant changes that alter the validity of a study or expose subjects to different risks. Examples requiring prior approval are as follows: (1) significant increase in dosage, frequency, or route of administration of the drug; or (2) increase in the number of subjects participating over the initial maximum number judged adequate to reach a conclusion on the drugs, benefits, or risks.

Accurate and adequate periodic reports to the sponsor on progress of the investigation enable the sponsor to collate and review data, to obtain an overall view of the study, and to provide useful information back to the investigators as well as to FDA in the annual progress report. Investigators are obligated to report progress annually to the sponsor and to submit a final report within 3 months of the end of the clinical investigation. Reports should include communications with an IRB, receipt and disposition of drugs, the protocols and any modifications, individual subjects' records, and reports on the investigation. The case report form should contain clinical study and follow-up data abstracted from the prior medical history and clinical study medical history. The latter are maintained by the investigator as back-up data. The investigator is required to retain copies of these records for 2 years following either approval of an NDA or discontinuation of the IND.

In addition, the investigator is required to submit a special report for any serious, unusual adverse effect, life-threatening problem, or death that may reasonably be regarded as caused by or associated with the drug and that was not previously anticipated by the sponsor (e.g., routine or minor side-effects noted in the sponsor's brochure for investigators). These special reports are to be submitted as soon as possible but no later than 10 working days after discovery.

The investigator is responsible for informing human subjects that a drug is experimental and obtaining written informed consent. The investigator must submit the proposed clinical investigation to an IRB for review. IRB approval must be obtained before human subjects are allowed to enter the study. The investigator has the responsibility to submit all proposed changes in the investigation to the IRB for approval before implementation unless the change is being mode to reduce or eliminate risk to the subjects; must respond to IRB requests; and must report to the IRB within 10 working days of detection of any ADRs, life-threatening medical problems, or death. The investigator must report annually in progress on the investigation, and within 3 months after completion, termination, or discontinuation of his/her protocol or the entire study.

An investigator shall permit an investigative drug to be administered only to subjects who are under his/her personal supervision or under the supervision of another investigator responsible to him/her who is listed in forms FD 1571, 1572, or 1573. An investigator shall not supply the drug to any other persons for use without prior authorization of the sponsor.

An investigator shall maintain adequate and accurate records showing the receipt and disposition of all supplied drugs including quantity received and administered, identification of the subjects, and disposition of unused drugs.

An investigator shall not promote an experimental drug as safe and effective for the purpose for which it is under investigation.

An investigator shall permit authorized FDA employees or authorized representatives of the sponsor to inspect records of the clinical investigation for the purposes of verification of case reports or other information prepared for the sponsor for submission to FDA. Copies of the records may be made from which identifying information has been deleted or, without deletion, if FDA has reason to believe that informed consent or case reports are false or misleading.

VII. INVESTIGATIONAL NEW DRUG DISTRIBUTION AND INVESTIGATORS

The system by which the NCI distributes drugs for research in cancer chemotherapy is complex and is undergoing change to improve control and accountability. It must account for drugs during several stages of research and clinical development. The concern of the Task Force in the drug distribution area centered about whether NCI drugs were being distributed to only registered investigators, whether they were being used for the intended purposes, and whether drugs distributed could be accounted for.

NCI's cytotoxic drug distribution is to facilitate cancer research and to treat cancer patients. The size of the NCI cytotoxic drug distribution program is indicated by the following figures: approximately 100 requests for drugs are received per day; approximately 5,000 physicians are eligible to receive the drugs at any time; and approximately 1,000 requests per year for "compassionate IND" drug use are received. The number of new patients being studied in protocols each year is approximately 37,000. Investigators administer approximately 70 investigational anticancer drugs (40 under intensive investigation).

The NCI drug distribution system is located within IDB. The drug acquisition, formulation, packaging, shipping, and inventory elements are located within the Pharmacetical Resources Branch (PRB), DTP, DCT, NCI.

Classification of Investigation New Drugs and Investigators

For purposes of distribution, each investigational new drug is classified as being in Group A, B, or C, or their subcategories (see Figure 5).

Group A Drugs

Group A , "A one" is the designation for drugs undergoing Phase I studies to identify types and severity of the drug's toxicity, to identify the maximally tolerated dose for specific dosing schedules, and to determine the clinical pharmacology and pharmacokinetics. The Phase I trials are conducted by the Phase I Working Group, which consists primarily of 10 Phase I contractors as follows:

Phase I Working Groups

. Sidney Farber Cancer Center
. Memorial Sloan-Kettering Cancer Center
. Mayo Clinic
. M. D. Anderson Hospital and Tumor Institute
. Mt. Sinai Hospital
. University of Kansas Medical Center
. Vermont Regional Cancer Center
. Wayne State University
. Georgetown University School of Medicine.
. University of Wisconsin Hospitals

The PIs responsible for the conduct of these first clinical studies in humans are oncologists with additional expertise in clinical pharmacology and are generally regarded as leading cytotoxic drug investigators.

Figure 5

CHARACTERISTICS OF

INVESTIGATIONAL NEW DRUG DISTRIBUTION

NCI's DRUG GROUP	FDA's IND PHASE *	INVESTIGATORS	FUNDING SOURCE	NUMBER OF INSTITUTIONS/ PRINCIPAL INVESTIGATORS (PI)	ESTIMATED NUMBER OF ACTIVE REGISTERED INVESTIGATORS	ESTIMATED NUMBER OF NEW PATIENTS PER YEAR	ACTIVE CYTOTOXIC DRUGS
A_I	I	Phase I/II Working Group	IDB Contract primarily	10 Phase I Working Groups 7 - 10 Ad Hoc PIs	100-150	1,000	6
A_{II}	Early II (single agent in Tumor Panels)	Phase I/II Working Group	IDB Contract primarily	10 Phase I Working Groups 7-10 Ad Hoc PIs 8 Phase II/III Contracts	(100-150) 26	4,000	5
B_I	Mid II, Late II (wider) III	Clinical Cooperative Groups	CIB Grants/ Cooperative Agreements	13 Phase II/III Contractors 15 Cooperative Groups	II 75 III 240 PIs 1,000 Institutional 1,000 Satellites	II 4,000 (Phase II) III 23,000	12
B_{II}	Late II, III	Cancer Centers	Core Grants-(Division of Resources, Centers, and Community Activities, NCI)	56 Cancer Centers	4,000	4,000	10 (1) B_{III} No new studies; 5 - B_{IV}: IND being closed)
		New Drug Studies Groups	Unfunded	10 New Drug Studies Groups			
C	Comparable to Post-marketing Surveillance ("IV")	"Properly Trained Physicians"	Unfunded	1,500 Registered Investigators	1,500	Unknown *** (100,000)	7
"Special Exception"	Compassionate IND"	Oncologists in above Institutions	-	Variable	Variable	1,000 ****	-
					5,000	37,000 **	40 *

* These IND Phase designations are approximations of the major IND Phase corresponding to NCI's drug group classification. A drug may be at the Phase II stage of development in one type of cancer, and Phase I or later stages in other types of cancer.

** In addition, about 40,000 patients continued on study who were entered in protocols in earlier year.

*** Group C program does not require patient-by-patient reporting.

**** Approximately 1000 orders were for compassionate INDs. Approximately 1000 orders were received in FY 1981 from physicians requesting a Group C drug for the first time.

* These 40 are being studied actively; a total of approximately 70 INDs are formally open.

Generally, five or six drugs per year are tested in Phase I, involving a total of about 1,000 new patients participating in about 25 to 30 protocols. The Phase I contractors might have two active Phase I drug protocols each involving approximately 25 patients. Typically, the research team would include two or three co-principal investigators (generally full-time senior faculty), three to five registered investigators (generally full-time junior faculty), and five to seven oncology fellows acting under supervision of the full-time faculty. A large contractor like M.D. Anderson might have four to six different active Phase I drug protocols and 50 registered investigators and 50 fellows active at any one time, however.

In addition to the Phase I contractors, approximately seven to ten qualified investigators may be selected by the Chief, IDB, to perform specific Phase I studies on an ad hoc basis. These ad hoc investigators are chosen because of specific expertise or experience with the particular drug to be tested. Often they have played an important role in the preclinical development of the drug.

Group A_{II}, "A two" is the designation for drugs undergoing early, single agent Phase II studies in six to ten specific signal tumors to estimate the frequency of clinical response and safety of the drug. Clinical studies with A_{II} drugs are conducted by members of the Phase I Working Group designated to perform Phase II studies and also by several Phase II/III contractors. The Phase I Working Group contractors designated to conduct Phase II studies typically have five to ten registered investigators and 10 - 20 fellows. Generally, five to seven new drugs are added yearly to A status. At any time, an additional 10 to 15 drugs from earlier years might be still in A_{II} in late stages of completing the signal tumor panels. Approximately 75 - 85 percent of the Phase II studies are early Phase II studies performed by these A_{II} clinical studies (six - 10 panels often with two dosing schedules involving 14 to 25 patients per study, frequently with independent replications).

Group B Drugs

Group B is the designation for drugs undergoing both subsequent single agent Phase II trials and late Phase II multiple-agent or multiple-modality studies in signal tumor panels to estimate effectiveness. Also, Phase III trials comparing the efficacy of one therapeutic plan, including the investigational new drug, against another therapeutic plan are carried out under the Group B designation. The focus of the clinical trials is determining the role of the drug in the therapy of specific neoplastic diseases. A drug is moved from A_{II} to B_I status in a specific disease after the IDB-directed evaluation in one or more signal tumors has indicated that a specific dosing schedule is tolerated by patients and there is evidence of disease responses. The CIB, CTEP, is administratively responsible for the clinical investigation, but IDB remains responsible for the drug-oriented aspects of the studies.

Although Phase I Working Group members and Phase I/II contractors perform research with Group B drugs, the vast majority of these late Phase II/III clinical trials are performed by investigators in clinical cooperative groups (funded through CIB grants, contracts, or cooperative agreements), comprehensive or clinical cancer centers (core grant supported by the Division of Resources, Centers, and Community Activities, NCI) and non-NCI funded New Drug Studies Groups.

The cooperative clinical study groups are groups of clinical investigators consisting of university and cancer center physicians who pool their scientific resources and patients with the objective of carrying out multicenter collaborative investigative clinical trials encompassing all cancer diagnoses and multiple therapeutic disciplines including surgery, radiotherapy, and chemotherapy. Over the past 25 years, the cooperative groups have evolved methods to study new cancer therapies attempting to improve the quality of research and clinical care. They have developed mechanisms for the organization and administration of cooperative groups, selection of investigators, elimination of nonproductive or incompetent investigators, quality control, monitoring for safety and efficacy, providing statistical support, and reporting of results to NCI and the cancer treatment community. Generally, these elements are present in all groups.

Organizationally, each group has an administrative/operations office headed by the group chairman elected from one of the member institutions. This office is responsible for protocol development; patient record maintenance; reporting and collection of unusual or unexpected toxicities; and communication between the investigators, the protocol study chairman, and NCI. Each group has a central statistical support office with full-time academic statisticians. For scientific activities, the groups have modality committees (including surgery, radiotherapy, chemotherapy, immunotherapy), pathology and pharmacology committees, and disease site committees (including breast, gynecology-genitourinary, gastroenterology, head and neck, hematology, lung, melanoma, and so on). These committees are responsible for assisting in the development of protocols, conducting group studies, and reviewing the presentation of results.

Groups have varying numbers of member institutions. Each has a PI responsible for the institution's activities. Clinical study protocols are generated by the PIs in close collaboration with the scientific committees and statistical office. The PI serves as study chairman for the group.

Most of the clinical cooperative groups have about five to eight cooperating institutions, although some of the larger groups have 15 or more institutions. The composition and geographical location of these groups is presented in a document entitled, "Membership Roster, Cancer Clinical Trials Groups and Projects," available from the CTEP, DCT, NCI. There are now approximately 240 PIs of cooperating institutions. Five to 20 junior and senior faculty work with each PI as registered co-investigators. They are experienced chemotherapists, radiotherapists, and surgeons who span the range of medical and surgical specialists involved in adult and child oncology and hematology. There are an estimated 1,000 registered co-investigators in the cooperative groups. Numerous oncology and hematology fellows-in-training, oncology nurses, and data managers assist the co-investigators.

Table 2

Clinical Cooperative Groups

A. Grant Program

Multimodality Multidisease Groups

- Cancer and Leukemia Group B (CALGB)
- Eastern Cooperative Oncology Group (ECOG)
- North Central Cancer Treatment Group (NCCTG)
- Northern California Oncology Group (NCOG)
- Southeastern Cancer Study Group (SEG)
- Southwest Oncology Group (SWOG)

Multimodality Groups Devoted to a Major Oncologic Area

- Children's Cancer Study Group (CCSG)
- Gynecologic Oncology Group (GOG)
- Pediatric Oncology Group (POG)

Single Modality Group

- Radiation Therapy Oncology Group (RTOG)

Single Disease Groups

- Intergroup Ewing's Sarcoma Study (IESS)
- Intergroup Rhabdomyosarcoma Study (IRS)
- National Surgical Adjuvant Breast and Bowel Project (NSABP)
- National Wilms' Tumor Study Group (NWTG)
- Polycythemia Vera Study Group (PVG)
- Radiotherapy Hodgkin's Disease Group (RHDC)

Special Activities Groups

- Clinical Coordinating Center for Statistics (CCC)
- European Organization for Research on Treatment for Cancer (EORTC) Operations and Statistical Office
- Lymphoma Pathology Reference Center (LPRC)
- Radiologic Physics Center (RPC)

B. Contract Programs

- Gastrointestinal Tumor Study Group (GITSG)
- National Surgical Adjuvant Breast and Bowel Project (NSABP)
- Phase II-III Drug Evaluation Contracts for Solid Disseminated Tumors
- Lung Cancer Study Group
- Instituto Nazionale por le Studio e la Cura dei Tumori
- WHO Melanoma
- Phase II Gastrointestinal Cancer
- Ovarian
- Chemoprevention of Cervical Cancer
- Pediatric Phase I-II Task Order
- Surgical Section: Head and Neck Contracts Program

C. Miscellaneous

Intergroup Testicular Study
NCI-Pan American Health Organization: Collaborative Cancer Treatment Research Program (PAHO:CCTRP)
VA Surgical Oncology Group (VASOG)

Table 3

CLINICAL AND COMPREHENSIVE CANCER CENTERS AND NEW DRUG STUDIES GROUPS

Alabama: University of Alabama Comprehensive Cancer Center*

Arizona: University of Arizona Cancer Center**

California: University of Southern California/LAC Cancer Center*
UCLA Comprehensive Cancer Center*
Northern California Cancer Program**
University of California - San Diego**

Colorado: Colorado Regional Cancer Center, Inc.*

Connecticut: Yale University Comprehensive Cancer Center*

District of Columbia: Georgetown University/Howard University
Comprehensive Cancer Center*

Florida: Comprehensive Cancer Center for the State of Florida*

Georgia: Emory University Cancer Center**

Hawaii: University of Hawaii at Monoa**

Illinois: Illinois Cancer Council*
Northwestern University Cancer Center*
University of Chicago Cancer Research Center*
Rush Cancer Center**

Kansas: Mid-America Cancer Center Program**

Kentucky: Ephramin McDowell Community Cancer Network**

Maryland: Johns Hopkins Oncology Center*

Massachusetts: Sidney Farber Comprehensive Cancer Center*
Boston University Cancer Research Center**
Tufts-New England Medical Center**
Clinical Cancer Center

Michigan: Michigan Cancer Foundation*

Minnesota: Mayo Comprehensive Cancer Center*

Missouri: Missouri Cancer Programs, Inc.**

New Hampshire: Norris Cotton Cancer Center of the
Dartmouth-Hitchcock Medical Center*

*Comprehensive Cancer Center
**Clinical Cancer Center
***New Drug Studies Group

New Mexico: University of New Mexico Cancer Research and Treatment Center**

New York: Memorial Sloan-Kettering Cancer Center*
Roswell Park Memorial Institute*
Albert Einstein College of Medicine Cancer Research Center**
Hospital for Joint Diseases and Medical Center**
Mount Sinai School of Medicine*
Columbia University Cancer Research Center*
New York University Medical Center Clinical Cancer Center**
University of Rochester Cancer Center**

North Carolina: Duke University Comprehensive Cancer Center*
University of North Carolina Cancer Research Center
Bowman Gray School of Medicine Oncology Research Center**

Ohio: The Ohio State University Comprehensive Cancer Center*
The Cancer Center, Inc.**

Oklahoma: Oklahoma Cancer Center**

Pennsylvania: Fox Chase/University of Pennsylvania Comprehensive Cancer Center*

Puerto Rico: Puerto Rico Cancer Center**

Rhode Island: Roger Williams General Hospital**

Tennessee: Memphis Regional Cancer Center**
St. Jude Children's Research Hospital**

Texas: The University of Texas System Cancer Center, Houston*
University of Texas Health Science Center, Dallas**
University of Texas Medical Branch, Galveston**

Vermont: Vermont Regional Cancer Center**

Virginia: Medical College of Virginia, Virginia Commonwealth University, Cancer Center**

Washington: Fred Hutchinson Cancer Research Center*

Wisconsin: University of Wisconsin Clinical Center*
Medical College of Wisconsin**

*Comprehensive Cancer Center
**Clinical Cancer Center
***New Drug Studies Group

Stanford University Medical Center***

American Cancer Research Center and Hospital***

The University of Iowa College of Medicine***

Hahnemann Medical College and Hospital***

The Milton S. Hershey Medical Center***

Vanderbilt University***

University of Louisville Cancer Center***

National Naval Medical Center***

Indiana University Medical Center***

The Natalie Warren Bryant Cancer Center***

*Comprehensive Cancer Center
**Clinical Cancer Center
***New Drug Studies Group

Affiliated with the primary hospitals are community hospitals and physicians' offices, termed satellites. There are an estimated 500 to 750 satellites. Affiliated investigators are usually practicing oncologists and hematologists who often attend group meetings and whose patients participate in protocol studies. Being an affiliated satellite investigator permits a practicing oncologist to be aware of the current research advances and allows his/her patients newest chemotherapies and other treatment modalities. In the past, affiliated satellite investigators were listed on the principal or co-investigator form FD 1573 and requested drugs through them to the cooperative group operations office. In recent months, affiliated satellite investigators also have been required to submit form FD 1573 registration for protocols in which they are participating.

The cooperative groups primarily conduct clinical trials with drugs in the B_I classification. Currently, there are 12 B_I drugs. The groups perform 15 - 25 percent of the Phase II studies (late Phase II studies), involving approximately 4,000 patients. In addition, the cooperative groups' Phase II studies involve a significant majority, probably over 80 percent, of the estimated 30,000 newly treated Phase III patients yearly.

Over the years, each group has developed a character of its own. Some emphasize a specific treatment modality, a particular disease, or a defined age group. Several of the larger groups stress multidisease programs involving all therapeutic modalities.

There are two categories of cooperative groups. The first is composed of 15 groups which have been supported by peer reviewed grants. In the second category are approximately 12 groups consisting of individual Phase II/III contractors who are experienced in selected diseases and who function as a small cooperative group. These are coordinated by CTEP project officers and carry out targeted pilot studies with combination agents and modalities (See Table 2).

Group B_{II} drugs are available under a New Drug Studies mechanism to allow investigators who are not supported either by a CTEP grant or contract to carry out innovative studies of investigational new drugs which IDB believes are of demonstrated safety and effectiveness from prior studies. Currently ten drugs are in Group B_{II} classification. The institutions that may use Group B drugs are 56 comprehensive cancer centers and clinical cancer centers approved for support by the Cancer Center Support (core) Grant ("P-30") and 10 other institutions which are approved by IDB as New Drug Studies groups (See Table 3). These studies are performed under the NCI's INDs but are not usually NDA-directed. NCI has delegated to the cancer center or New Drug Studies Group director the authority to approve protocols of investigators in their institutions or affiliated investigators within the geographic area. Protocols, forms FD 1573, and a list of cooperating investigators are submitted to IDB by the investigators. IDB reviews these protocols only for safety, qualifications of investigators, and human subjects protection. The precise number of investigators or patients participating in these studies is not readily known by CTEP. Generally, the cancer centers' and New Drug Studies Groups' studies involve less than 20 percent of the Phase II patients.

Group C Drugs

During the evaluation of investigational drugs by DCT, NCI, certain drugs were found to have a role in the treatment of specific tumor types. There is often a long time period before these drugs are sponsored by the pharmaceutical industry and receive NDA approval. In the interim, to allow patients with these diseases to have the benefit of this drug therapy, a Group C drug classification has been developed. A secondary purpose of this distribution is to acquire more information on safety of the drug being used as it likely will be used in clinical practice after marketing; essentially this is a Phase IV-like post-marketing study.

Group C drugs are supported by evidence of reproducible relative efficacy in a tumor type, alter the pattern of care of the disease, and can be safely administered by properly trained physicians without requiring specialized supportive care facilities, as judged by available abstracts, papers, and reports in the IND. A drug has relative efficacy in treatment of a specific tumor if the frequency of objective response (usually defined as a decrease of greater than 50 percent of the product of two perpendicular dimensions of a measurable tumor) is at least as good as the response rate produced by the most effective commercially available agent for that tumor at a comparable point in the therapy of the disease. Response rates over 25 percent in refractory diseases qualify as showing evidence of relative efficacy even if several other agents of similar efficacy are available. Group C drugs are provided to physicians who have registered via form FD 1573 for the treatment of individual patients who qualify under the conditions of "the guidelines" for the drug.

The procedure for Group C classification is as follows: (a) "Guidelines for Clinical Use" for a given tumor and supporting data are submitted to the FDA for review and approval; (b) review of materials by the FDA is conducted so that no more than 3 months elapse between the request and acceptance or rejection of the request by the FDA Oncologic Drugs Advisory Committee; (c) the drug remains in Group B for further/different research studies (e.g., on other tumor types), even when advanced to Group C for a particular tumor.

Criteria for Group C classification include the following: (a) evidence of safety and relative efficacy in the treatment of a specific cancer type in the form of published abstracts, papers, and reports to the NCI; and (b) impact on the pattern of care of patients with the specific doses that are safely administered by properly trained physicians without requiring specialized supportive care facilities. Approval does not require demonstration of increased patient survival rates. This approval is not tantamount to securing formal FDA NDA approval of effectiveness for this indication.

Currently, seven cytotoxic drugs are in Group C. In addition to all the investigators registered for Groups A and B drugs, approximately 1500 physicians are registered to treat patients under the Group C guidelines. In addition, nonregistered physicians may obtain these drugs through associations with investigators at cancer centers or elsewhere.

EXHIBIT

[illegible] **NATIONAL INSTITUTES OF HEALTH**
NATIONAL CANCER INSTITUTE

CLINICAL DRUG REQUEST

RETURN COMPLETED FORM TO:
Drug Regulatory Affairs Section
Division of Cancer Treatment, NCI
Landow Building, Room C419
7910 Woodmont Avenue
Bethesda, Maryland 20014, U.S.A.

The drugs listed below are requested for the use of:

Dr. ____________________ No. ________

Requestor (if other than investigator) ____________________

Title ____________________ Tel ________

INSTRUCTIONS
Please read instructions on reverse before completion of this form.

FOR NCI USE ONLY

ORDER NO

DATE

SIGNATURE OF AUTHORIZING OFFICIAL

TITLE

TYPE ALL ENTRIES - ONE ITEM PER LINE

PROTOCOL OR IND NUMBER	No. Pt. *		NSC NUMBER	DRUG NAME	STRENGTH & DOSE FORM (Specify capsules, tablets, vials)	QUANTITY (Specify bottles or vials)	MANUFACTURER	LOT NO.	Comments
		A							
		B							
		C							
		D							
		E							
		F							
		G							

* Number of patients currently on study   Signature   Date

PLEASE SPECIFY AFFILIATION
1 ☐ Study Group ____________
2 ☐ Contract
3 ☐ Phase I Working Group
4 ☐ Cancer Center ____________
5 ☐ NCI Intramural
6 ☐ International Agreement
7 ☐ Group C (Guidelines)
8 ☐ Nonclinical Use
9 ☐ Other ____________
(Specify, i.e. Foreign, Independent, etc.)

Shipping Address Must Be Typed In Space Below

REMARKS
☐ Routine Request
☐ Emergency Request
☐ Other ____________

SHIPPING INFORMATION

DATE SHIPPED

HOW SHIPPED

1 ☐ Room Temperature
2 ☐ Refrigerate on Arrival
3 ☐ Packed in Dry Ice
4 ☐ Airmail
5 ☐ Special Delivery
6 ☐ OTHER

Pulled By	Checked By	Packaged By

1. PHARMACEUTICAL RESOURCES BRANCH

"Compassionate INDs"

Almost 1,000 new patients yearly are treated by oncologists, generally investigators in cooperative groups and Phase I/II working group, with investigational drugs under a "Special Exception" granted by IDB. These are essentially "compassionate INDs" for Group B drugs not yet approved for Group C and are approved on a case-by-case basis. Were there not a Group C status which allows these drugs to be distributed, there would be large numbers of additional patients who would be able to obtain needed therapy only by the "compassionate IND" mechanism.

Distribution To Investigators

Clinical Drug Request forms (NIH-986) are supplied to each investigator. (See Exhibit in this section.) The investigator submits the form via the group operations office if a member of a cooperative study group, and the request is received and logged in. The request is certified by comparing it with computerized files of approved protocols and registered investigators for the following specific items, termed "criteria data":

1. Is the investigator registration form FD 1573 on file?
2. Is the investigator's name, address, and registration number correct?
3. Is the protocol number correct and is the protocol status appropriate (i.e. approved, not approved, active, or inactive)?
4. Is the drug specified on the protocol?
5. Is the drug dosage form appropriate for the protocol?
6. Are the quantity ordered and ordering frequency reasonable?

Only after the drug request is verified by the above is the drug quantity authorized by an IDB staff member and the drug shipped by NCI's PRB.

For Group C drugs being used for therapeutic purposes alone and not as part of an experimental protocol, physicians' requests are accepted only for the disease conditions specified in the Clinical Guidelines. Registration via form FD 1573 is required and reviewed, and the physician is required to obtain informed consent from the patient and IRB approval. The physician is required to report serious or unexpected ADRs via form FD 1639a, Drug Experience Report, Short Form. (See Section IX, Adverse Drug Reactions.) Because of the limited scientific value of such drug use, physicians are encouraged to join existing studies using the drug requested or to refer their patients to approved protocol studies.

Requests for drugs under the "compassionate IND" rubric (i.e., a Special Exception for treatment of a single desperately ill patient) are handled individually by NCI staff. A requesting letter from the physician, form FD 1573, and follow-up ADR reporting are required.

Experimental drugs also may be provided by NCI to investigators who wish to perform nonclinical (i.e., animal or in vitro) experiments. If the requirement is for simple bulk chemical, the request is dealt with by the Drug Synthesis and Chemistry Branch, DTP, DCT. If a formulated preparation is needed, the request goes to PRB. Whenever possible, formulated material originally intended for human use, but returned to the PRB without having been used, is provided as a matter of economy. If such preparations are not available, or not suitable for the intended study, special formulations may be made up by PRB. Whichever of the above alternatives applies, the material is shipped with clear labeling that identifies it as not for human use.

Task Force Comments and Recommendations

With the described drug distribution mechanisms in place and the confidence that they were being used routinely, the Task Force was satisfied that NCI has a policy and procedures which ensure that drugs are being distributed directly only to registered investigators for valid purposes and that proper records and files of shipments are kept. The system can generate reports of all investigators who have received a given drug, of all drugs a given investigator has received, and of all investigators working on a given protocol.

Recommendations -

NCI should require

1. That all investigators including those affiliated investigators practicing in satellites of cooperative group institutions and cancer centers be formally registered by a form FD 1573 either as individual investigators or listed as under the personal supervision of the principal investigator and a specific IND number. (This information should be made available to FDA to permit inclusion of all NCI investigators using NCI supplied chemotherapy in its strategy for selecting investigators for routine investigations);

2. That all drugs provided under a specified protocol for human use but not used in accordance with that protocol be returned to NCI for proper handling by PRB, DCT, NCI;

3. That communication links about eligibility to receive drugs and drug usage be developed among PRB and the appropriate other branches of DCT to control drug distribution and leakage effectively; and,

4. That under circumstances of noncompliance with NCI's requirements or FDA's regulatory requirements, no cytotoxic drug be shipped from NCI to the investigator.

If the principal or clinical investigator is not in compliance with PRB requirements for anticancer drug control, PRB will be responsible for bringing the violation to the attention of the Director, DCT, for appropriate action.

Currently, investigators receive relatively little information from NCI about their responsibilities in handling the drug beyond that in the approved protocol and the requirements listed on the form FD 1573.

> Recommendation -
>
> NCI should develop a set of instructions or guidelines on drug-handling responsibilities of investigators to be sent out once a year to every investigator who files an updated or new form FD 1573.

NCI's ability to account for the distribution and use of a drug after it has been shipped is currently not satisfactory, but NCI has plans for remedying these deficiencies which will be implemented in early 1982. At the present time, there are a "return drug program" and a "recall program" to retrieve drugs at time of termination of INDs or individual protocols. There is, however, no way of documenting how unreturned drugs were actually used. In the plan to be implemented, investigators receiving drugs will be required to keep a detailed log showing the disposition of all medication received. This log would be "audited" at time of site visits by checking against clinical records to be sure the drug was used as recorded. Further, summary data from the log would be required to be submitted periodically to NCI where it would be stored on computer and the data used to check against investigators' progress reports. The computer record summary could be taken on site visits to be checked against the actual log. The proposed plan appears to be sound, reasonable, and likely to be effective.

> Recommendation -
>
> High priority should be given to implementing the proposed NCI plans as soon as possible to remedy what is viewed as a serious defect in the current drug distribution system. Requiring such logs and reporting should both dissuade investigators from misuse of drugs and readily identify the practice of "secondary" distribution of investigational drugs, that is, the transfer of drugs to physicians outside the regulated environment and the use of investigational drugs for unapproved purposes.

NCI has suggested that, in the future, distribution of Group C drugs will be restricted to the 200 CCOPs now being developed. This approach is likely to increase the concern of those who argue that NCI is using its drug distribution system to establish a controlled medical delivery system through the selection of a special group of physicians to receive new drugs. Another point of contention is the limited reporting required of physicians using Group C drugs; it is held that useful information about the efficacy and the limitations of these drugs is being lost because patients are "diverted" from protocol-directed studies, possibly delaying the accumulation of evidence needed to support an NDA. NCI feels that the Group C mechanism provides a means to respond to medical and public pressure for improving cancer therapy as quickly as possible without ignoring their responsibilities to ensure that physicians are sensititve to the risks in using these agents. NCI is also concerned about the problem of loss of information; staff will continue to encourage physicians to refer patients to study sites whenever possible and looks forward to the CCOP organizational structure as a way to reduce this loss.

Group C drug classification provides a useful mechanism for bringing these drugs which have demonstrated efficacy against a specific tumor type to the cancer patient on a wide basis.

Recommendation -

The Group C drug classification should be retained.

In one recent case of abuse that has attracted public attention, a drug that was not intended for human use was, in fact, given to patients without an IRB- or NCI-approved protocol and without FDA "approval" of an IND. The investigator has been disciplined after the fact, and the question has been raised whether or not such malfeasance could be effectively prevented by NCI by having tighter control on the distribution of drugs for preclinical studies. The Task Force believes that this approach is not practical, because - (1) drugs for preclinical studies have several sources within NCI, and may, in some cases, also be available in bulk chemical form from other sources; and (2) there is no way to prevent an investigator who intends to violate regulations entirely from requesting drugs for animal use and then submitting some record to indicate that he/she did use the material in that way. Animals, unlike human patients, do not have an independent hospital record against which research records can be checked for veracity. It is believed to be much more practical to rely on education, clear labeling of materials not approved for human use, and significant disciplinary action in the rare case of willful violation of the law this regard.

In summary, the anticancer drug distribution controls are adequate for the task of ensuring accountability. Drug leakage will be controlled by the procedures now being implemented by NCI. Further, the monitoring of investigators and institutional records will significantly increase the sensitivity and commitment of investigators to see that anticancer drugs are used for the intended protocol and that unused drugs will be returned properly and in a timely manner to PRB.

VIII. NCI INVESTIGATOR-SPONSOR ROLES: AN ALTERNATIVE

The Task Force discussed an alternative for implementing parts of the NCI cytotoxic drug development program. Some members of the Task Force had reservations about the alternative and the perspectives undergirding it. The Task Force was unable to reach consensus and makes no recommendations concerning this alternative. The analysis and perspectives on NCI investigator-sponsor roles that led to the alternative proposal are presented along with some members' differing views.

The Alternative Proposal -

The proposed alternative is intended to - (1) lead to more rapid drug development culminating in an approved NDA; (2) reduce NCI's responsibilities as IND sponsor for the large number of clinical trials which are not primarily focussed on a drug's NDA-oriented clinical assessment, and (3) reduce the number of drugs and length of time drugs remain in Group C status before becoming marketed products. To accomplish these goals, a differentiation of NCI's roles is required leading to more focussed and defined drug development activities.

NCI should increase the focus on its drug development role by greater central planning, organization, and monitoring of investigational drug studies emphasizing definitive conclusions on safety and efficacy. To facilitate completion of necessary NDA-directed studies, NCI should consider acting as IND sponsor only for NDA-directed studies. NCI would then no longer serve as IND sponsor for non-NDA-directed, knowledge-directed studies. Field investigators in cooperative groups and cancer centers initiating and conducting these nonpivotal Phase III studies would be IND sponsor-investigators of their own studies. The sponsor-investigator would he responsible for interacting directly with FDA on these studies rather than through NCI staff.

NCI, in response to its Congressional mandate to develop an anticancer drug program, has evolved over the past decade to a position unique within NIH. NCI can be seen as having three distinct roles in the cytotoxic drug area - scientific research, cancer treatment, and drug development.

Scientific Research Role

NCI's primary mission is to facilitate scientific research and knowledge attainment to understand, prevent, diagnose, and treat cancer -- "knowledge directed studies." In this role, the clinical trials research program develops combinations of drugs which are effective in multimodality treatment of a particular type of cancer. These studies are currently performed in "late" or "wide" Phase II and Phase III under NCI's INDs with drugs in the Group B distribution classification. In this role, NCI serves as a supporter and facilitator of important field investigator-initiated clinical trials similar to the research of other NIH Institutes.

Cancer Treatment Role

In its second role, the clinical trials research program serves as the nidus around which a controlled nationwide treatment system providing investigational cytotoxic drugs to cancer patients has formed. It consists of clinical-investigators in prestigious cancer centers and affiliated community hospitals, and practicing oncologists. This controlled delivery system was intended to transfer rapidly the newest therapeutic and diagnostic technologies from the researchers to practicing oncologists to patients. Thus, DCT has become the major source of nonmarketed Groups B and C drugs for the treatment of cancer patients.

Drug Development Role

As NCI's cytotoxic drug research program expanded and evolved over the past decade, the Institute acquired additional functions usually performed for other classes drugs by pharmaceutical firms. NCI has, by default, become the major anticancer drug developer with a mission to discover, develop, and establish safety and efficacy of new anticancer drugs. Thus, DCT is the major sponsor for investigational cytotoxic drug studies. In this role, the comprehensive preclinical and clinical development of a drug is carried out to ensure that drugs made available to cancer patients are safe and effective. For non-cytotoxic drugs, availability occurs through marketing following approval of an NDA submitted by a pharmaceutical firm. For cytotoxic drugs without an industry sponsor, NCI now achieves wide distribution through Group C status but might, if necessary, submit an NDA.

The studies encompassed in this role are (1) all preclinical screening and toxicity testing; (2) all the basic Phase I and Phase II trials which establish a safe dosage schedule, study of the drug's toxicity, and the magnitude of effectiveness for specific tumors in humans; and (3) finally selected "pivotal" Phase III studies which definitively establish the safety, effectiveness, and role of the drug in the therapy of neoplastic disease in broader patient populations approximating future intended medical use. Thus, clinical trials performed under the sponsor's IND and directed toward obtaining approval of an NDA permitting marketing, i.e., "NDA-directed studies," are conducted in NCI's drug development role. All Group A drug testing can be considered NDA-directed. Single agent tumor panel studies with Group B drugs are also NDA-directed.

Over the past 5 years, NCI has increased its role as the major cytotoxic drug developer. NCI is the IND sponsor for the vast majority of clinical studies with these agents and has assumed a more active central role in direction of these studies. NCI should continue to increase this focus on its drug development role. Increased central organization, planning, and monitoring emphasizing definitive studies on safety and efficacy may lead to more rapid drug development, and submission and approval of an NDA allowing marketing.

Current Management of NCI's IND Studies

NCI's sponsor responsibilities, with the required information processing and reporting to FDA, are the same for both "NDA-directed" and "knowledge-directed" studies conducted under NCI's INDs. Both the NCI scientific research role and its drug development role could be better served by different emphasis already implicit in the design of the drug group classification and associated administrative procedures. Investigators using Group A drugs are performing NDA-directed studies; those using Group B drugs are doing knowledge directed studies; and practicing oncologists use Group C drugs primarily for treatment.

NCI appears to have patterned its drug development system after that used by the pharmaceutical industry. A relatively small number of investigators in Phase I/II Working Group perform Phase I and single agent tumor panel studies with Group A drugs, which are most often under NCI contract. These investigations are directed and closely evaluated and monitored by the IDB Drug Monitor Team. Study progress is formally presented by the investigators to the sponsor at Phase I Working Group Meetings three times a year and at New Drug Liaison Meetings (Phase II) twice a year. A complete and comprehensive annual scientific progress report summarizes in detail all clinical studies performed. Since 1980, individual patient data are routinely collected from these investigators, formatted, monitored for clinical findings, and presented to the IDB Drug Monitors under the CTMS contract. With this current system, the quality of the Phase I/II data resembles that of industry and should be acceptable by FDA for an NDA.

In contrast, NCI administrative procedures utilized for investigators using Groups B and C drugs in studies performed in the cooperative groups and cancer centers and also the New Drug Studies Groups are different. Currently, about 85 percent of the patients treated in NCI-sponsored anticancer drug clinical trials are in these non-NDA-directed knowledge development studies. These are primarily supported by research grants and cooperative agreements. CIB staff manage those studies, allowing IDB staff to direct, monitor, and evaluate these investigations in a less intensive manner than studies with Group A drugs. The research done by these investigators should be considered in a similar category as that performed by other NIH research grantees.

Proposed Changes and Implications

As described previously on page 59, the proposed alternative is that NCI should increase the focus on its drug development role by greater central planning, organization, and monitoring of investigational drug studies emphasizing definitive conclusions on safety and efficacy. FDA already has investigational new drug procedures which distinguish pharmaceutical firm-sponsored INDs from physician-sponsored INDs. When an investigator wishes to act as sponsor for use of a drug solely as a research tool, a simple, abbreviated form of IND submission is acceptable. Studies of a drug that no manufacturer is interested in sponsoring, so called "orphan drugs," are frequently handled in this way by other researchers supported by NIH and the Alcohol, Drug Abuse and Mental Health Administration. The physician sponsoring this form of IND deals directly with FDA. This procedure is currently in use by several investigators in cancer centers or cooperative group institutions with drugs supplied to them directly by a pharmaceutical company or, infrequently, by NCI.

Under the proposed alternative, NCI support and assistance to field investigators would not be diminished. NCI would continue to supply drugs for these studies and permit these investigators to reference NCI's INDs for chemical, manufacturing, animal toxicity, human toxicity, and relative effectiveness data necessary for

IND approval. In exchange, NCI would continue to exercise the right of prior approval of protocols before distributing the drug and continue to require annual progress reports, including patient accrual and interim results and prompt reporting of unexpected ADRs. As at present, IDB and CIB would continue to have all the information necessary for scientific and programmatic analysis of all ongoing trials.

The proposed alternative would shift some current NCI responsibilities as IND sponsor to the oncology treatment community itself for non-NDA directed studies. FDA would deal with these as they do with other sponsor-investigator initiated IND studies. IDB would no longer be responsible for on site verification of individual patient data, detailed protocol monitoring, direct ADR reporting to FDA, nor direct coordination of the numerous investigators in the cooperative groups and cancer centers. Thus, a considerable administrative burden and responsibility would be removed from NCI with no loss in scientific function of NDA-related activities.

A significant current gap in drug development impeding NDA approval is the relative paucity of controlled comparative clinical trials in which the specific activity of the investigational drug can be isolated from the multidrug and/or multimodality therapy so that specific drug efficacy could be definitively established. With more NCI direction of pivotal Phase III trials, NCI could ensure that these classic NDA-directed Phase III clinical trials are routinely performed by the cooperative groups. Performance of these drug focussed controlled comparative clinical trials will be facilitated by conversion of cooperative group support from grants to cooperative agreements beginning in 1981.

To facilitate compilation of data in a future NDA, IDB should develop and require use of a centralized, uniform data system for reporting, organizing, formatting, and analyzing all NDA-directed studies. All targeted NDA-directed studies should be subjected to similiar monitoring and review as the Phase I/II Working Group data.

Group C Drugs

NCI should continue to be the IND sponsor for Group C drugs. NCI would continue to distribute these investigational drugs to community oncologists registered with NCI as investigators to acquire safety information in the context in which the drug is likely to be used in clinical practice after marketing, e.g., essentially "postmarketing" surveillance studies. Although the Group C distribution mechanism is a useful and valuable interim means of transferring new drug technology to the community, oncologists and cancer patients would be better served by having proven safe and effective agents marketed for use so they are available in hospitals and pharmacies under physicians' prescriptions.

The Group C drug distribution mechanism is useful as an "institutionalized compassionate IND procedure." However, it is recognized that this drug distribution mechanism is a deviation and exception from the policy that all physicians have the authority to prescribe "approved" drugs. Further, the criticism that Group C drugs are approved for broad distribution for treatment with less detailed and definitive evidence than required for NDA-approved drugs cannot be contradicted as long as a different approval procedure is used by FDA.

This valuable drug distribution mechanism was conceived to bridge the gap between the times when efficacy and safety was demonstrated to the satisfaction of some, and an NDA was approved constituting the official mechanism for drug distribution. However, since NCI has not been highly successful in attracting commercial NDA sponsorship for a number of Group C drugs, the mechanism has been expensive to maintain (while not useful from a research perspective) and has been seen by some as a permanent solution for distribution of some cytotoxic drugs. To remedy this situation, NCI should take the steps necessary to move drugs from Group C to NDA status as quickly as possible by conducting definitive NDA oriented studies or serving as the NDA sponsor of last resort. If these steps are built into the planning of a drug's development, the additional cost to NCI to accomplish reaching NDA status may not be great.

Potential Difficulties With the Alternative Proposal

Members of the Task Force offered the following criticisms of the alternatives:

A. Requiring investigators to submit their own INDs for late Phase II and most Phase III studies may - (1) make it more difficult for NCI to carry out broad review and coordination of the development of anticancer therapy including cytotoxic drugs by fragmenting responsibility for oversight; (2) fail to relieve NCI of much administrative burden; (3) slow research on cytotoxic drugs by making it more difficult for individual investigators to initiate studies; and (4) overtax FDA staff with large numbers of INDs.

   1. Coordination of the complex process of cancer therapy development is desirable so as to minimize duplication and delay. Currently, NCI's capability to do such coordination exceeds that of FDA. Relinquishing the IND sponsor role would take away some of the authority from NCI for obtaining responses from the investigators who would be holding their own INDs and shift responsibility for monitoring and coordination to FDA. This shift would lessen a much needed activity.

   2. NCI would still be responsible for reviewing and approving protocols under the proposed plan. Because NCI does not now audit data in late Phase II and Phase III studies, the new plan would not lessen its responsibility for data verification.

   3. Some investigators may be inhibited from initiating useful research because of the added burden of submitting a separate IND to FDA. The ability to reference NCI's INDs will lower, but not eliminate, this hurdle.

   4. FDA staff, already heavily taxed in their review of cytotoxic drug development, will be further burdened by the need to review many additional INDs.

B. As cytotoxic drugs are given to increasingly large numbers of cancer patients it becomes increasingly important to demonstrate that the drugs are adequately safe and efficacious. Marketing that follows NDA approval and the closed controlled Group C distribution are the two routes by which cytotoxic agents reach large numbers of patients. Emphasis should be placed on reconciling the differences in current criteria used and establishing greater similarity of criteria for approving these two drug categories. The alternate proposal would foster deliberate "NDA-directed" studies and emphasize discrepancies that now exist between Group C and marketed drugs.

C. Until much less toxic and more effective anticancer chemical agents are available, it may indeed be better for the public to not emphasize the NDA marketing route but to maintain the controlled distribution to patients via qualified physicians as now occurs with Group C distribution.

D. Implementation of the alternative proposal may not alter the reluctance of industry to submit NDAs for cytotoxic drugs. The alternative does not change the major underlying reasons for cytotoxic agents being "orphan" drugs.

In summary, an alternative proposal for NCI-Investigator Sponsor Roles has been presented. The feasibility of this approach requires additional consideration. The Task Force was unwilling to take a position on the alternative, in part because it was unable to evaluate evidence which might clarify the possible advantages and disadvantages.

IX. ADVERSE DRUG REACTIONS

General definitions that have been used for ADRs include the following: (1) a reaction to a drug serious enough to cause real or potential permanent injury or death; (2) a reaction which is noxious and unintended; and (3) a reaction which is unpleasant, disabling, or deadly. There is no agreement on an exact working definition of ADRs or even on the dimensions of the problem. Definitions that are useful for some drugs are not appropriate for the anticancer drug testing program. Both the toxicity of anticancer drugs and physical condition of cancer patients present special problems in identifying ADRs. The individual physician plays a critical role in recognizing the possibility of an ADR in a situation when highly toxic substances are given to terminally ill patients.

Requirements for reporting of untoward findings are found in FDA regulations and on investigators' registration forms, as follows. NCI as a sponsor has this responsibility.

NCI Responsibilities -

> Sponsors of INDs "...shall promptly investigate and report to the Food and Drug Administration and to all investigators any findings associated with use of the drug that may suggest significant hazards, contraindications, side effects, and precautions pertinent to the safety of the drug. If the finding is alarming it shall be reported immediately and the clinical investigation discontinued until the finding is adequately evaluated and a decision reached that it is safe to proceed." [(21 CFR 312.1(a)(6)] form FD 1571, Notice of Claimed Investigational Exemption for a New Drug.

Investigator Responsibilities -

> "Any adverse effects that may reasonably be regarded as caused by, or probably caused by, the new drug shall be reported to the sponsor promptly, and if alarming, it [sic] shall be reported immediately." form FD 1573

The MeCCNU experience reflected serious problems regarding ADR reporting. First, clinical investigators suspecting an adverse reaction associated with MeCCNU failed to report their concern immediately to NCI. Instead, some investigators were working up possible ADRs and writing findings for medical journals. Second, NCI, after receiving several reports of renal failure possibly associated with the drug, failed to report these incidents immediately to FDA. Instead, NCI was working up suspect ADRs and waiting to confirm association with the drug before reporting to FDA. (See Section III, A Review of Two Cases Concerning NCI's Anticancer Drug Program.) These failure pointed to critical misunderstandings on the part of investigators and NCI about requirements of ADR reporting with investigational new drugs.

NCI has recently revised its procedures for ADR reporting and evaluation, as depicted in Figure 6, "Current NCI Procedures for Addressing Adverse Drug Reactions Reported to Them by Clinical Investigators in the Cancer Chemotherapy Program."

In an October 1981 letter to all clinical investigators, NCI reminded them of their ADR reporting responsibilities including the obligation to report immediately by telephone to NCI any alarming reaction to an investigational drug. In addition, NCI has confirmed its intention to report alarming reactions immediately to FDA and to all clinical investigators. The role of NCI is that of an expert who can collect, synthesize, interpret various ADR reports, and make a judgment as to whether or not a serious problem is appearing.

The ultimate responsibility of FDA is to ensure through the reporting mechanism that this judgment is properly made and acted upon. At FDA, adverse reactions to investigational new drugs are routed to FDA reviewing medical officer for evaluation. If the reviewing medical officer finds the ADR provocative or alarming in nature, the sponsor, such as NCI, may be contacted for more detailed information. Reactions may be of such a potentially serious nature and the grounds to suspect causality so compelling as to merit a limited or even a complete suspension of clinical studies. The investigational regulations provide for termination of an IND if -

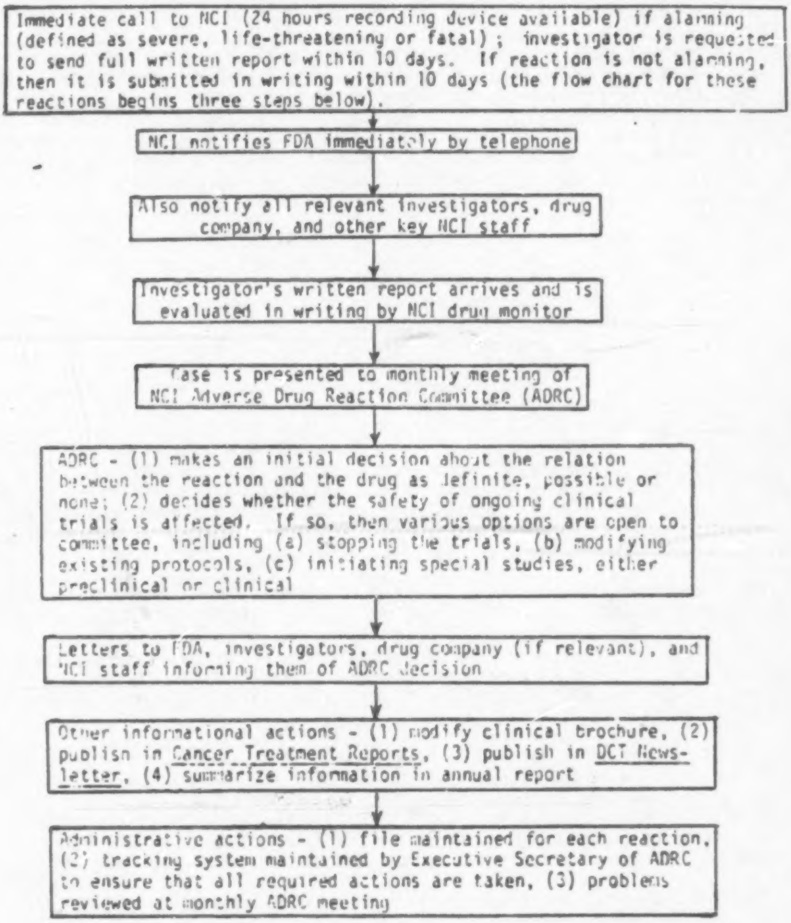
> "...the sponsor fails promptly to investigate and inform the Food and Drug Administration and all investigators of newly found serious or potentially serious hazards, contraindications, side-effects, and precautions pertinent to the safety of the new drug;"

While the new system has clearly defined responsibilities and required actions of both investigators and NCI, problems still remain with regard to identifying accurately those reactions which are clearly associated with a drug. Since anticancer drugs cause serious side-effects and since most patients are desperately ill and have many serious medical events caused by their illness, the problem of identifying ADRs with anticancer investigational drugs is particularly difficult.

Any ADR reporting system has to balance sensitivity with discrimination. If sensitivity is set extremely high, both NCI and FDA will be flooded with possible ADRs, and the job of identifying the true ADR will be virtually impossible. A real difficulty is with the state-of-the-art available to separate and quantify the ADR from the many other events and reactions that cancer patients on research protocols are experiencing.

The Task Force has noted what appears to be an inconsistency between a literal reading of the regulations and the actual practice of NCI and FDA in reporting "alarming" ADRs and, as a result, discontinuing clinical investigations.

ADVERSE DRUG REACTION REPORTING



Immediate call to NCI (24 hours recording device available) if alarming (defined as severe, life-threatening or fatal) ; investigator is requested to send full written report within 10 days. If reaction is not alarming, then it is submitted in writing within 10 days (the flow chart for these reactions begins three steps below).

NCI notifies FDA immediately by telephone

Also notify all relevant investigators, drug company, and other key NCI staff

Investigator's written report arrives and is evaluated in writing by NCI drug monitor

Case is presented to monthly meeting of NCI Adverse Drug Reaction Committee (ADRC)

ADRC - (1) makes an initial decision about the relation between the reaction and the drug as definite, possible or none; (2) decides whether the safety of ongoing clinical trials is affected. If so, then various options are open to committee, including (a) stopping the trials, (b) modifying existing protocols, (c) initiating special studies, either preclinical or clinical

Letters to FDA, investigators, drug company (if relevant), and NCI staff informing them of ADRC decision

Other informational actions - (1) modify clinical brochure, (2) publish in *Cancer Treatment Reports*, (3) publish in *DCT Newsletter*, (4) summarize information in annual report

Administrative actions - (1) file maintained for each reaction, (2) tracking system maintained by Executive Secretary of ADRC to ensure that all required actions are taken, (3) problems reviewed at monthly ADRC meeting

Figure 6. Current NCI Procedures for Addressing Adverse Drug Reactions Reported to Them by Clinical Investigators in the Cancer Chemotherapy Program

NCI
12/81

Regulations require that a sponsor report alarming reactions immediately and discontinue clinical investigations. NCI has been reporting ADRs immediately to FDA, but neither has automatically discontinued clinical trials. While the current state of affairs may simply represent overuse of "alarming" ADR reporting procedures, it creates the appearance of noncompliance with the literal language of the regulation. Furthermore, despite what the regulation states, it may not always be practical or desirable to discontinue clinical trials because of an alarming ADR.

Accordingly, the Task Force believes that the regulation should be reviewed and consideration be given to making it more flexible with regard to the discontinuation of the clinical trial. In the interim, NCI and FDA should confer and better define the word "alarming" as presently used.

The Task Force found that FDA and NCI modifications in ADR reporting stress the importance of timely reporting of ADRs and outline the subsequent steps that are taken with the determination of a possible or confirmed ADR. These steps may include alerting investigators, making changes in protocols and informed consent forms, and putting a hold on the IND.

The Task Force found that NCI's procedures and management practices are adequate to encourage reporting of findings from the investigator; to work-up the determination of a questionable, suspect, or confirmed ADR; and to respond to FDA requirements in a timely manner.

In addition, the Task Force found that FDA procedures and management practices are adequate to monitor the ADR work-up; to respond to reported ADRs; and within the state-of-the-art available, to ensure the protection of cancer patients from unsafe drugs.

X. THERAPEUTIC INTENT

The Task Force heard widely disparate views on whether "therapeutic intent" exists in the initiation and conduct of Phase I clinical trials involving cytotoxic drugs. The Task Force understands this phrase to mean an intention, in some degree, to improve or to stabilize the condition of a specific patient to be inducted into a research protocol.

It is important that such an intent exists. Because the drugs used are so aversive, and because the patients are so dependent and vulnerable, it is more difficult to justify ethically Phase I cancer trials if there is no therapeutic intent.

There is no doubt that the medical community involved in the development of cancer drugs believes that there is a real and substantial therapeutic intent involved in the initiation and conduct of Phase I trials. Members of the medical community note that - (1) subjects are recruited into protocols only if they are terminally ill and conventional treatment has failed; (2) drugs are used only after animal testing has shown evidence of anticancer activity and review has deemed a drug to be promising; and, (3) since 1975, there has been an overall response rate of approximately 9.5 percent in Phase I trials.

On the other hand, critics point to the fact that preclinical animal testing is of little predictive value relative to particular human cancers, that response rate figures include minimal responses that should not be considered therapeutic in any real sense, and that, therefore, while there may be some small hope of benefit to patients, generally any benefit which occurs to a specific patient is mere "happenstance."

Two points confuse this discussion. First, there is a perception that a trial cannot be both therapeutic and experimental. The Task Force believes that perception is wrong. While in some cases an investigator may be interested solely in acquiring generalizable knowledge (as is the case when dealing with normal volunteers with other classes of drugs), when dealing with terminally ill patients and drugs which have shown some anticancer potential, it is possible to pursue both therapeutic and experimental goals. In fact, true singleness of purpose may be difficult to find even when physicians administer accepted drugs from their offices to patients to evaluate the impact of the drug not only for the effect on a particular patient but also for the usefulness of the drug on other patients.

The more difficult problem exists when a tension [illegible] between the pursuit of experimental goals and the pursuit of therapeutic goals. For example, it may be that after initial doses of a certain cytotoxic drug, it becomes apparent that the toxicity in a patient is no longer acceptable, but that it is not clear that studies of the drug should be abandoned. Even in this case, conflict is avoidable. In such an event, the patient may be removed from the trial, but the trial may continue with additional patients. The second point of confusion is that Phase I trials are characterized by FDA procedures themselves as being for the purpose of establishing toxicity. [See for example, 21 CFR 312.1(a) form FD 1571]. For most Phase I trials, which involve solely normal volunteers, that characterization is correct. The case, however, is significantly different in Phase I cancer trials. Drugs are administered to sick patients to help them combat illness. To ignore that difference and merely point to a general characterization of Phase I trials is inappropriate.

On the basis of its deliberations, the Task Force has concluded that the real issue before it is not whether some measure of therapeutic intent exists in Phase I trials - clearly, for the reasons set out above, it is possible to establish such an intent. Rather, the concern is whether the low probability of response and the risk of toxic effects of the drug are made clear to the patient through the informed consent process.

We have heard considerable evidence that desperately ill patients are anxious to enter Phase I trials as a last resort. While the Task Force recognized that people do not have an absolute right to harm themselves consciously, neither should they be absolutely precluded from seeking treatment which holds out hope of benefit. If patient or family choice is to be the determinative factor, however, then ensuring that such a choice is a reasonably informed one is critical. A special problem in achieving informed consent in Phase I cancer trials is the physical condition of the patient and desperation of the patient and family. Thus, attention must be given not only to the information being conveyed, but also to whether the information is being "heard," or undue influence of physician on patient exists. Although there are extensive regulations governing the consent process as it relates to experiments involving human subjects, both NCI and FDA officials admitted that they have no means for ascertaining whether the actual interaction between the patient and the physician is conducted in an appropriate manner (see section on Protection of Human Subjects).

In summary, the Task Force found that therapeutic intent exists in Phase I trials. This conclusion acknowledges that - (1) the patients receiving the investigational drugs are terminally ill, and conventional treatment has failed; (2) these drugs are administered to patients only after animal testing has demonstrated evidence of anticancer activity and screening has shown a drug to be promising (although the validity of the screening process has not been proven); and, (3) since 1975, there has been an overall response rate of approximately 9.5 percent in the cancer patients receiving new anticancer drugs.

XI. PROTECTION OF HUMAN SUBJECTS - INFORMED CONSENT AND IRBs

The clinical investigator, IRBs, institutions, NCI, FDA, and the Office of Protection from Research Risks (OPRR), all have responsibilities to protect human subjects of research through the use, review, and monitoring of consent and investigative procedures.

Informed Consent - Background

The doctrine of informed consent to all medical procedures has evolved from the autonomy which Anglo-American common law bestows on the human body. With certain exceptions, each person has the right not to be touched or treated medically without authorization. There is much case law defining the scope of patients' rights to informed consent in medical treatment.

Recent court decisions have expanded the concept of informed consent. In *Cobbs v. Grant* 8 Cal. 3d 229, 502 P.2d 1(1972), the California Supreme Court addressed the notion of physician's discretion to withhold information. The Court found, "It is the prerogative of the patient, not the physician, to determine for himself the direction in which he believes his interests lie. To enable the patient to chart his course knowledgeably, reasonable familiarity with the therapeutic alternatives and their hazards becomes essential." (Cobbs, *supra*, at 242-243). Sufficiency of information is also addressed in *Canterbury v. Spence* 464 F. 2d 772 (D.C. Cir. 1972), cert. denied, 409 U.S. 1064 (1972). The Canterbury Court defined "true consent" as a choice based on the opportunity to evaluate available options and risks and flatly rejected the notion that disclosure of risk be discretionary with the physician. The standard has evolved even further since the 1972 cases and now requires full disclosure in all but the exceptional cases [see *Dessi v. United States*, 489 F. Supp. 772 (E.D. Va. 1980); *Rogers v. Okin*, 634 F. 2d 650 (1st Cir. 1980), *cert.* granted, 49 U.S.L.W. 3779 (April 21, 1981)].

Three basic elements are necessary for informed consent -- adequate information to understand risks and benefits, competency of the patient to make a decision, and the freedom of the patient to decide without coercion. Research in the area of informed consent highlights the difficulty and complexity of the process and provides no conclusive evidence that informed consent is or is not feasible for medical patients.

The following summary of research findings in the area of informed consent has been compiled from two recent articles, "What We Do and Do Not Know About Informed Consent: An Overview of the Empirical Studies," Meisel, Alan, J.D. and Roth, Loren H., M.D., M.P.H. - *Journal of American Medical Association*, November 27, 1981, Vol 246, No. 21; and, "Informed Consent and Competence - A Review of Empirical Research," Stanley, Barbara H., Ph.D. - presented at a National Institute of Mental Health Workshop on Informed Consent, January 12, 1981, (National Technical Information Services, U.S. Department of Commerce, Document No. PB 81-235285).

Stanley points out that the majority of published articles on the consent process have been opinion or position papers. Empirical studies which have been conducted, are often marred by problems of study design -- including failure to report what was actually disclosed in the informed consent process, equating recall with comprehension, thus, not allowing for the normal forgetting process, use of hypothetical situations instead of real patients facing real decisions, and problems of bias when the investigator is also the physician for the subjects.

For the purpose of this section, the conclusions on research of competence of the patient have been excluded. Highlights of research will be summarized for two areas - (1) patient reactions and understanding; and (2) decision-making. Although disclosure and voluntariness are also essential to the informed consent process, there are few studies in those areas.

Patient Understanding and Reactions

Many studies assessing patient understanding do not include a detailed description of the information conveyed to the patient or the complexity of language used in the consent procedures. In general, studies show the patient's comprehension level of consent information is not high, and no convincing evidence exists that any medium is more effective than any other (e.g., video tapes). Greater instruction appears to be associated with greater understanding, and patients given a chance to discuss the informed consent form understood better than those who just read the form (Williams, 1977). Cassileth et al. (1980) concluded that ambulatory patients showed greater comprehension of consent information (for treatment, not research) than bedridden patients. Other studies focussing on research patients show that understanding of research procedures may be more problematic for acutely ill patients. Defects of studies include failure to describe amount of instruction, assumption that recall of consent information can be equated with comprehension and difficulty of comparing conclusions derived from studies with patients of varying degrees of illness and normal volunteers.

Contradictory conclusions have been reached regarding patient reactions to consent information. In one study (Alfidi, 1971), patients "appreciated" disclosure but were made less comfortable by it. Several other studies (Denney et al., 1975; Lankton et al., 1977; Houts and Leaman, 1980) found no difference in patient anxiety level. In one study, patient anxiety levels were lower postoperatively for patients who were better informed (Denney et al., 1975).

Stanley cautions about separating normal anxiety about making a decision regarding a medical procedure from anxiety caused by detailed information. She suggests that future studies in this area should focus on finding the least anxiety-producing manner in which to disclose information.

Decision-making

Many studies on decision-making in the informed consent process utilize volunteers whose responses may be different from patients. Studies relating comprehension to decision-making seem to indicate that higher levels of comprehension are associated with higher rate of consent. For these findings to be meaningful, however, one would have to know the risks and benefits of procedures studied.

Meisel and Roth point to the need for studies to examine the "complex relationships between what patients are told, what they understand of this information, how and whether they use it in making a decision, and whether they consent to or refuse treatment."

Conclusion

There is a paucity of well designed empirical studies of the informed consent process; further study is necessary. The methodological difficulties with existing studies, the lack of studies regarding certain aspects, the often contradictory or inconclusive results, and the elusive nature of certain elements of informed consent underscore the complexity of the informed consent procedure and issues around these procedures.

Problems with Informed Consent for Cancer Patients

There are still many questions and concerns about the adequacy for informed consent for terminal cancer patients requested to participate in research with investigational new drugs.

At the House of Representatives Hearing chaired by Representatives Waxman and Gore on October 27, 1981, Dr. Gail Povar, clinical internist and teacher of medical ethics at George Washington University, described the particular problems of informed consent with cancer patients. According to Povar, patients asked to participate in Phase I trials are vulnerable to coercion because of the certainty of death without a new treatment. Dr. Povar questioned whether these fearful, angry, and desperate people are, in fact, free to choose. She further explored the impact of the doctor/patient relationship on the informed consent process, and the doctor's inherent desire to do something. She concluded that all these factors affect the objectivity of the information conveyed, the specific competency of the patient, and the freedom to choose.

A contrasting view on informed consent was expressed in the Hearing record by oncologist Dr. Solomon Garb, himself a cancer patient:

> "Informed consent is as adequate as human ingenuity can make it. The problem is not in the informed consent form or in what the doctor tells the patient, but in what the patient understands or is willing to understand. Obviously, I knew that cancer protocols can produce all kinds of side effects, some of them lethal, but I also knew that the outlook for stomach cancer had been dismal. I just skimmed over the form I signed. As a patient, my key question was, and is--'Doctor, if you had my illness would you want this treatment for yourself?' When the answer was 'yes,' I signed. I don't think that the informed consent procedure is a serious problem."

Some individuals feel that cancer patients (particularly those in Phase I trials) are extremely vulnerable and need special assistance in giving informed consent because of their physical condition, their anxiety (which may affect the ability to understand information disclosed), the extreme toxicity of anticancer drugs, and the small possibility of significant benefit. Those individuals studying the informed consent process in a variety of medical treatment and research situations have offered suggestions to minimize the possibility of coercion on the part of the physician and to enhance the decision-making capacity of the patient through a variety of special mechanisms, including utilizing a third party to present or to discuss the information, utilizing a patient advocate, allowing time between disclosure of information and patient decision, and testing patient understanding of consent information.

The cancer patient faces extremely difficult treatment decisions in traditional and research situations. It is crucial, therefore, that patient decisions be made on the basis of complete and frank information. In Phase I trials, for example, the physician disclosing information to the potential research participant must be particularly careful to describe fully "reasonably forseeable risks and discomforts," "any benefits to the subject or other which may reasonably be expected," and to include a statement that "participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled." (HHS 45 CFR 46.116) The Task Force concurs that information disclosed for Phase I must include a statement about the small possibility of direct benefit to the patient him/herself.

The informed consent form and process should reflect the different proportions of risks and benefits anticipated as the investigational new drug passes from the first use in human subjects in Phase I through Phases II, III, and beyond. Some Task Force members felt that the patient should also be told how many subjects had preceded him/her in the protocol and what the results were.

IRBs - Background

The IRB is the body designated by an institution to ensure the protection of human subjects through initial and continuing review of research proposals. It is composed of members of diverse backgrounds charged with reviewing ethical and risk/benefit aspects of clinical research involving human subjects to ensure that - (1) the rights and welfare of human subjects are adequately protected; (2) the methods used to obtain informed consent are adequate and appropriate; and (3) the risks to the subjects are outweighed by the sum of the potential benefits to the subject and the importance of the knowledge to be obtained. The IRB tasks are difficult ones; IRB members may face pressure if they disapprove research projects which could bring money to their institutions or if they disapprove projects proposed by senior colleagues.

Evidence from FDA site visits and past studies of IRBs suggests that IRBs are not succeeding completely in preventing abuses. This is particularly troublesome when considering cancer research where the subjects are very ill. As noted in "The Belmont Report"* in an overall discussion of the ethical principles for

---

*Ethical Principles and Guidelines for the Protection of Human Subjects of Research, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, DHHS Publication No. (OS) 78-0012.

HISTORICAL REVIEW OF EVENTS RELATING TO PROTECTION OF HUMAN SUBJECTS IN RESEARCH/INFORMED CONSENT

	HHS	FDA	OTHER
1949			The Nuremberg Code - voluntary consent - risk/benefit - subject free to end experiment - avoid unnecessary suffering
1962			Drug Amendments to FD&C Act - informed consent must be obtained from human beings receiving investigational drugs or serving as controls
1963		FDA regulations adopts standard practice regarding informed consent from 1962 amendments - allows for exceptions when not feasible when, in investigator's professional judgment, contrary to best interests of subjects	
1964			Declaration of Helsinki - concerns for interest of subject must always prevail over the interest of science and society
1966	HHS/PHS-wide policy of informed consent in Federally funded research		
1967		FDA regulations - informed consent must be obtained from subjects (or their representatives) in all Phase I studies of investigational drugs (in writing) - oral consent may be obtained in Phase III if physician decides it's necessary or preferable	
1971	HHS-wide policy on informed consent	FDA requires initial and continuing review by Institutional Review Committee for institutionalized patients	
1974	HHS regulations for protection of human subjects	FDA initiates IRB inspections	National Research Act PL 93-348 - mandates review of biomedical and behavioral research by IRB - creates National Commission

	HHS	FDA	OTHER
1974-1978			National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
1975			Revision of Helsinki Accord
1976		FDA Bioresearch Monitoring Program funded and organized	GAO Report-- "Federal Control of New Testing Is Not Adequately Protecting Human Subjects And The Public"
1977		DSI, BD, FDA established	
1978		Sponsor - Monitor regulations proposed	
1978		FDA published proposed standards for IRBs and clinical investigators	National Commission publishes its recommendations 43 FR 56174
1979	HHS published proposed rules for protection of human subjects; 44 FR 47688	FDA withdraws its Aug. 8, 1978, proposal submits 44 FR 47699 to obtain more uniform agency-wide requirements for informed consent	
			Sen. Kennedy hearings on bioresearch monitoring (Subcommittee on Health and Scientific Research)
1981	HHS publishes regulations	FDA publishes regulations	President's Commission for the Study of Ethical Issues of Medicine and Biomedical and Behavioral Research
			Rep. Gore hearings on ethical and institutional considerations of biomedical research (Subcommittee on Investigations and Oversight - House of Representatives Committee on Science and Technology)
	HHS regulations(45 CFR 46) effective	FDA regulations (21 CFR 50; 21 CFR 56) effective	Reps. Waxman/Gore hearings on NCI (Subcommittee on Investigations and General Oversight and Subcommittee on Health and the Environment - House of Representatives Committee on Science and Technology)
			Sen. Hawkins hearing on NCI (Subcommittee on Investigations and General Oversight - Senate Senate Labor and Human Resources Committee)

the protection of human subjects, vulnerable populations face particular problems as subjects of research, as follows:

> "One special incidence of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition."

HHS/FDA POLICIES AND REGULATIONS REGARDING INFORMED CONSENT

Policy and regulations regarding informed consent and IRBs have evolved in HHS for almost 20 years. A brief summary of the major changes regarding informed consent in the Department, along with reference to key outside activities which have effected that process, is outlined in the Figure 7.

Current Regulations

Since July 27, 1981, HHS and FDA (which has its own regulatory authority) have had almost identical regulations regarding the requirements for IRBs and informed consent for participants in research. This ends a long period in which HHS and FDA had different regulations in these areas. Now, the eight elements of informed consent in the two sets of regulations are identical with one exception; there is a provision in the FDA regulations in the discussion of confidentiality of records that FDA may inspect the medical records.

HHS 45 CFR 46.116 (a)

(a) Basic elements of informed consent. ...in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

A complete HHS/FDA Regulation Comparison is available in the Office of Health Affairs, FDA.

Current regulations require that each institution which wishes to receive HHS funding for research covered by the regulations must have an IRB to review that research. The IRB membership must have a broadly based membership and must carry out the review responsibilities set forth in the regulations. FDA has also for a number of years had parallel requirements calling for IRB review of research involving human subjects and investigational drugs.

Implementation of Regulations

The differences in the application of the current regulations by NIH and FDA stem from their different roles. NIH supports research and uses a mechanism by which an institution assures that it will follow HHS regulations. If performance is unacceptable, NIH can withdraw acceptance of an institution's general assurance (explained in the following) or withdraw funds from a particular project. FDA, as a regulatory agency, has not adopted the general assurance mechanism; instead, it guarantees the safety of human subjects through inspection and audit activities and can use sanctions such as disqualifying the IRB, institution, or investigator when poor performance is found.

Since the inception of the FDA Bioresearch Monitoring Program (BIMO) in June 1977, deficiencies in patient consent have been among the most commonly found problems in routine inspections of clinical investigators and IRBs. In a March 1, 1981, report, 28 clinical investigators surveyed had inadequate patient consent forms. Two percent failed to obtain informed consent. Of 187 IRB inspections carried out in fiscal year 1980, approximately 100 were deficient in their informed consent review in one way or another. While there are no indications of what the deficiencies actually were, only four were classified as "official action indicated" (indicating serious noncompliance) and 30 were classified as "voluntary action indicated." The remaining 153 received "no action" letters, essentially educational letters suggesting improvements.

Analysis of 110 FY 1981 IRB inspections (for BD only) revealed 20 percent had mild deficiencies in informed consent; 14 percent had moderate deficiencies on this area; and 3 percent had severe deficiencies.

Problems continue to plague the IRBs and their performance. A specific example were the findings of an investigation by FDA on March 20, 1981, of the IRB at the M.D. Anderson Hospital and Tumor Institute. That evaluation revealed some commonly encountered problems. The M.D. Anderson IRB procedures for annual review of clinical investigations were found inadequate in that review of the project level did not ensure that each study had been reviewed. The IRB was not informed when a study had been terminated, and most importantly, information on ADRs and patient population and protocol changes were never brought to the IRB's attention.

Specifically in terms of NIH, FDA investigated IRB procedures at six institutes including NCI on November 20, 1980. At the completion of the investigation, FDA found that all of the institutes visited from November 18, 1980, through Feburary 2, 1981, had departed from regulations in two major areas. FDA regulations require that significant ADRs experienced by subjects of research be reported promptly to the IRB so the committee can decide if the study should be continued, revised, or terminated. It was noted, however, that in the intramural program at NIH, ADRs were reported to the Office of Medical Staff Affairs and to the Pharmacy Department and not to the NIH IRBs. These procedures have been modified recently to ensure that NIH IRBs are informed.

FDA regulations also require that reviews of an investigational new drug study will be conducted by the IRB at intervals appropriate to the degree of risk but not exceeding 1 year. This is to ensure that the research project being conducted is in compliance with the IRBs' understandings and recommendations. However, the IRBs for the intramural program at NIH were not conducting the required reviews of regulated studies. This has been corrected.

There is general agreement within the Task Force that the IRB, in principle, represents a critical force in ensuring the protection of human subjects in cancer investigations and other aspects of patient health care interaction. There is reason to believe, however, that the experience of IRBs has been marked by numerous problems, failures, and inconsistencies. Part of this is directly related to the absence of specific direction and education of members. With the passage of virtually identical IRB and informed consent regulations by HHS and FDA (which has separate regulatory authority) in July 1981, it is anticipated that this clarification of duties and responsibilities will enable the IRBs to play a more meaningful role.

Roles and Responsibilities in the Protection of Human Subjects in NCI-Sponsored Research

Individuals, IRBs, institutions, and governmental entities have responsibilities to protect human subjects of biomedical and behavioral research.

Figure 8

PROCESS OF NCI REVIEW OF INFORMED CONSENT WITH PROTOCOL FOR PHASE I TRIALS

Clinical Investigator (writes informed consent form)

↓

IRB (reviews and approves form and description of process, signs form HHS 596)

↓

Principal Investigator (submits informed consent form with protocol and form HHS 596 to IDB)

↙

NCI

↓

Drug Monitor IDB (for that specific drug) (reviews protocol and informed consent)

↓

Supervisory Drug Monitor (reviews protocol and informed consent)

↓

Chief, IDB (reviews protocol and informed consent)

↓

Associate Director, CTEP (review and sign off)

↓

Clinical Director, DCT (review and sign off)

↓

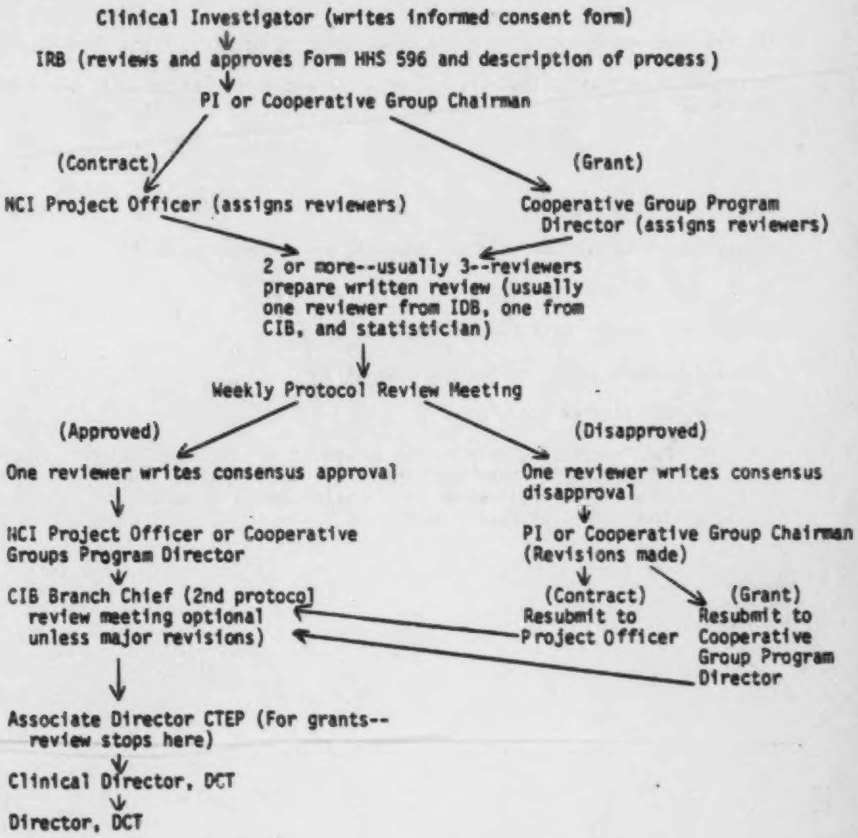
Director, DCT (review and sign off)

↘

FDA (protocol with informed consent form sent to Division of Oncology and Radiopharmaceutical Drug Products, FDA 1) with IND application for first protocol; 2) to IND jacket for subsequent protocols)

Figure 9

PROCESS OF NCI REVIEW OF INFORMED CONSENT WITH PROTOCOL FOR PHASE II, III


Clinical Investigator (writes informed consent form)
IRB (reviews and approves Form HHS 596 and description of process)
PI or Cooperative Group Chairman
(Contract)
(Grant)
NCI Project Officer (assigns reviewers)
Cooperative Group Program Director (assigns reviewers)
2 or more--usually 3--reviewers prepare written review (usually one reviewer from IDB, one from CIB, and statistician)
Weekly Protocol Review Meeting
(Approved)
(Disapproved)
One reviewer writes consensus approval
One reviewer writes consensus disapproval
NCI Project Officer or Cooperative Groups Program Director
PI or Cooperative Group Chairman (Revisions made)
CIB Branch Chief (2nd protocol review meeting optional unless major revisions)
(Contract) Resubmit to Project Officer
(Grant) Resubmit to Cooperative Group Program Director
Associate Director CTEP (For grants--review stops here)
Clinical Director, DCT
Director, DCT

In general, this is accomplished through the development and review of sound research proposals and informed consent procedures. The following section will outline briefly the general roles of the clinical investigator, the IRB, the institution, NCI, OPRR, and FDA in NCI-sponsored cancer chemotherapy research.

Clinical Investigator

The clinical investigator has the primary role in the informed consent process; he/she writes the informed consent form, submits it to the IRB and to NCI, presents the consent form to the patient, and fosters the ensuing discussions. The consent form by itself does not guarantee that informed consent is achieved. Informed consent is not a one time decision point, but rather an ongoing process which flows from the physician-patient relationship. It is ultimately the sensitivity, awareness, and skill of the physician which make possible an informed decision on the part of the patient.

The investigator is also responsible for reporting ADRs to the drug sponsor, for reporting unanticipated reactions to the IRB, and for modifying the consent process to reflect current information on ADRS.

Institutional Review Boards

The IRB reviews each research protocol, consent form, and description of the consent procedures. IRB approval (as evidenced by a signed form HHS 596, Protection of Human Subjects Certification) is necessary before the clinical investigator may submit the protocol to NCI and before clinical investigation may begin.

Institution

The institution gives assurance to the Secretary of HHS (OPRR is designated to accept the assurance) that all research funded by HHS will follow HHS regulations. As a condition of HHS's accepting this general assurance, the institution is required to establish procedures to safeguard rights of research subjects, including review by an IRB to determine the adequacy of protection. To provide additional safeguards, all NCI-funded grants are reviewed by NCI program personnel, and all investigator-initiated projects are subject to review by peers, by the national advisory boards and councils, and by OPRR. These reviews include specific attention to the adequacy of human subject protection.

NCI

The NCI staff have recently instituted new procedures requiring the enumeration of all the anticipated side-effects on the consent form. Several levels of staff within DCT review the consent form. Problems with the consent form are considered "major revisions" and require a revised protocol. The process is outlined on Figures 8 and 9.

Reviewers at each level approach the form globally (i.e., no one is assigned a particular aspect to review), utilizing their knowledge of the drug and their experience as investigators. None of the NCI review levels uses the elements of informed consent delineated in 45 CFR 46 in a systematic way to perform the review.

Regarding ADRs, NCI protects human subjects by informing both clinical investigators in the field and FDA of suspected ADRs. There is not an automatic follow-up to see if the consent form is modified after a new ADR is recognized. In some cases of reported ADRs (e.g., DHAD), NCI has required changes in the consent form to include mention of the additional anticipated toxic reactions.

There is evidence of recent increased attention by NCI reviewers to the consent form. In fact, a look at five recent protocols reviewed by NCI between October 14, 1981, and October 28, 1981, showed that reviewers of four recommended additions or changes in the consent form. Several NCI staff members confirmed that there has recently been more emphasis on and concern with the informed consent forms submitted with protocols.

NCI does not routinely coordinate with OPRR regarding issues of informed consent, although it occasionally consults with that office about special situations.

Office of Protection from Research Risks (OPPR)

OPRR at NIH is the designee of the Secretary of HHS to accept general assurances from institutions and to implement the requirements of 45 CFR 46 regarding the protection of human subjects in research. OPRR was created as the Institutional Relations Branch (Division of Research Grants) in 1966 when a PHS-wide policy of informed consent was developed. Following the National Research Act of 1974, the office was reorganized to become OPRR in the Office of the Director, NIH. Since the 1981 regulations were promulgated, OPRR has been reviewing and updating all general assurances; it plans to review assurances at 3 year intervals; previously, an assurance, once accepted, was not routinely reviewed. OPRR also reviews and considers special assurances for projects proposed from institutions without a general assurance.

OPRR screens summary statements on research projects prepared by NIH initial review groups (approximately 10,000 grants per year deal with human subjects research) for compliance with 45 CFR 46.

The contracts and cooperative agreements reviewed in NCI committees provide the primary funding support for the NCI-sponsored investigational new drug studies. The Task Force is concerned that OPRR may not routinely receive summaries prepared for scientific merit review of contract proposals and grant and cooperative agreement applications assigned to NCI-based public advisory committees. Thus, OPRR review of human subjects protection in research may exclude most of the NCI-sponsored cytotoxic drug research program.

The Task Force believes that OPRR must ensure the scope of its review includes summaries of scientific merit reviews for contracts, grants, and cooperative agreements involving human subjects in the NCI cytotoxic drug development program.

OPRR responds to reports of noncompliance or violation of the rights and welfare of human subjects. That response may include inquiries or a more formal investigation including a site visit to address special problems. Most of the 21 site visits OPRR conducted in 1980-1981 were in response to specific problems. Based on findings, OPRR recommended appropriate action to NIH officials. Before 1980, OPRR site visits--approximately 58 from 1975-1980--were of a routine nature. The earlier site visits gave guidance regarding regulations, general problems with IRBs, and complex situations. Section 474(b) of the PHS Act mandates within the Department an educational program on ethical issues in connection with the research involving human subjects. In 1979, OPRR entered into an interagency agreement with FDA to provide jointly educational activities regarding protection of human subjects. A contract was let in 1980 to design and develop a nationwide education program on Departmental IRB and informed consent regulations. The first step was a series of workshops in the fall of 1981 for federal officials with administrative and program responsibility for human subjects research. In 1982, FDA and OPRR will sponsor a series of regional workshops for the extramural research community.

In addition to its ongoing activities, OPRR is planning further efforts to ensure protection of human subjects in research. These activities include - (1) selection and review of a sample of consent forms approved by IRBs; (2) further educational activities regarding protection of human subjects; (3) a memorandum of understanding between FDA and OPRR to specify cooperative activities including the systematic sharing of information on IRB inspection; and (4) an evaluation of educational activities undertaken thus far.

FDA

Two divisions within BD, FDA, deal with informed consent for participants in investigational cytotoxic drug research.

The Division of Oncology and Radiopharmaceutical Drug Products reviews the IND from NCI for the first protocol of an investigational drug for human subjects. In addition, consent forms for all subsequent protocols are submitted to the IND jacket, and FDA medical officers may recommend modifications. At any time, FDA can request NCI to include a toxicity warning in the consent form when FDA judges that the risk so warrants.

The Division of Scientific Investigations (DSI) in BD engages in routine and "for cause" inspections of clinical investigators, IRBs, and sponsors. These investigations focus, in part, on protection of human subjects.

In addition to inspection activities, FDA undertakes educational activities to disseminate information and to clarify policy for federal government officials, researchers, and IRBs in the field.

President's Commission -

The President's Commission for the Study of Ethical Issues of Medicine and Biomedical and Behavioral Research undertakes additional educational activities. This commission is currently developing and implementing pilot IRB inspection protocols, utilizing members of other institutions' IRBs on the inspection team. They are also planning the development of educational materials for IRB use.

In summary, while the physician and the IRB share primary responsibility for the adequacy of the consent process and the soundness of the research protocol, the institutions, NCI, OPRR, and FDA all have important roles in ensuring the protection of human subjects through compliance with and enforcement of HHS and FDA regulations. The Task Force believes that stricter adherence to the HHS and FDA regulations will improve the informed consent process.

Recommendations -

Additional steps should be taken to improve compliance with existing FDA and HHS regulations. They are as follows:

1. NCI and FDA reviewers of informed consent forms should become more familiar with the required elements of the FDA and HHS regulations and use a reference review guide that lists the required elements of the regulations to ensure that the consent forms are thorough and specific and are evaluated against the requirements.

2. Feedback from NCI and FDA review of informed consent forms should be made to IRBs and to investigators; FDA Bioresearch Monitoring inspections should categorize deficiencies in informed consent forms from site visits so that summary data can be compiled for educational activities and to provide needed feedback.

3. IRBs should encourage lay members to review consent forms to determine that language is understandable and not unnecessarily technical, and encourage all members to use a review guide for review of informed consent forms.

4. OPRR should develop an educational program for all participants in the consent process - sponsors, institutional representatives, and investigators - to spell out their respective responsibilities and methods to ensure maximum communication of the risks and benefits of participation in clinical trials.

5. OPRR should - (a) proceed to select at random and review consent forms approved by IRBs; (b) expand the current

review of grant summary statements for protection of human subjects to include NCI contracts; and (c) initiate reviews of investigators, IRBs, and institutions to determine adherence to regulations.

6. NCI should increase its operational ties with OPRR with regard to protection of the rights of cancer patients.

XII. COMPARISON OF FDA-NCI RELATIONSHIPS WITH FDA-INDUSTRY RELATIONSHIPS

The Task Force has encountered two broad interrelated areas of concern. The first is concern about the extent to which the FDA regulatory role toward the NCI is different from (i.e., more lenient or favorable than) its role toward industry; and, if different, whether justifiably so. The second concern is the effectiveness of communication within FDA, within NCI, and between these two organizations. Communication problems appear to play a major role in the conflicting views which appear to exist about the regulator role of the FDA toward NCI and toward industry. An attempt has been made to separate these two interrelated problems in this discussion, but reference to the following section on Communication Problems will augment and highlight the concerns discussed here.

Many statements have been made that, in the area of cytotoxic drugs, FDA "favors" NCI over industry -- that is, FDA is lax in its regulation of NCI. Others have denied such favoritism or leniency, stating that administrative and substantive program factors warrant differences in FDA's stance and action; and that these do not constitute favoritism, although they may be misinterpreted by some as such. Many issues relating to this broad concern are discussed in detail in other sections of this report and will be only briefly referenced here.

In the following presentations, the Task Force has drawn on its many discussions with NCI and FDA staff as well as upon written material submitted (e.g., agency documents, Congressional hearing transcripts). Selected examples of information obtained by the Task Force illustrate the problems. For issues that are included, views are provided from many organizational levels of FDA and NCI.

The Task Force has tried to convey with fidelity FDA and NCI staffs' views, by including them in paraphrased form. Although this inclusion is somewhat disjointed, and the Task Force disagrees with many of the views, the Task Force felt that the presentation would better convey the wide range of opinion concerning these important issues. Paraphrased comments of persons interviewed are set off and indicated with a different type style.

These differences in views highlighted some of the perception and communication problems for consideration by the Task Force. A large number of comments concerning allegations of poor performance were heard from staff at lower organizational echelons. Overall, the Task Force obtained a reasonable balance by the extensive interviews of staff at higher organizational levels and extensive study of documents provided by them (as reflected in the major preceding sections of this report).

Material referenced in this section and the comments deal only with the cytotoxic drug program of the NCI and not with any other drug area.

The factors underlying the concerns about possible inappropriate preferential treatment by FDA of NCI as compared with industry have been identified by those who have spoken to the Task Force and will be discussed in the following order:

A. Pre-1975 History

B. Establishment of Mechanisms to Obtain Better Interaction Between FDA and NCI

C. Administrative Letters and Actions Regarding NCI Receive Higher Level Attention than Those for Industry

D. Regulator to Regulatee Relationship of FDA and NCI

E. Does FDA Accept Lower Quality Work from NCI than from Industry?

   1. Is FDA less demanding for toxicology data for cytotoxic drugs than for other drugs? Of NCI than it is of industry?

   2. Does FDA accept lower quality experimental protocols from NCI than from industry?

   3. Does FDA require from NCI submission of fewer data than from industry?

   4. Does FDA require less chemical information and less evidence of agent purity from NCI than from industry?

   5. Does FDA require less and accept tardy documentation supporting INDs from NCI as compared with industry?

F. Does FDA Monitor NCI Less than It Monitors Industry?

G. Unique Character of NCI's Group C Drugs

A. Pre-1975 History

Prior to 1975, FDA had a lax regulatory stance in regard to NCI's cytotoxic drug program. NCI was often deficient in annual reports; distribution of drugs from NCI to investigators and subsequent redistribution to other investigators and practitioners was not well controlled. FDA did not correct these perceived deficiencies. In part, this FDA attitude stemmed from a view that NCI was partly research activity and partly industry-like in its sponsorship role. This description of the laxity of the regulatory role exerted by FDA over NCI prior to 1975 is acknowledged by many staff members of FDA and NCI at all levels.

Task Force Comment -

To some extent, the history of lax regulation of NCI by FDA taints current understandings of the current regulatory stance. Past history should be acknowledged, but is not necessarily relevant to present and recent past events. Movement by FDA toward a more vigorous regulatory stance in the past 6 years is clear and unequivocal. Weight should be given to the analyses described throughout this report of more recent history, present stances, and proposed future actions.

B. Establishment of Mechanisms to Obtain Better Interaction Between FDA and NCI

Over the last 5 years there has been greatly augmented opportunity for meetings between NCI and FDA staffs, and the planning, initiation, approval, and use of an NCI operational plan for its cytotoxic drug development program. This was implemented in part by submission of a DMF by NCI, and its acceptance by FDA and was buttressed by the MOU between the Director of NIH and the Commissioner of Food and Drugs. The MOU provides for close communication between NCI and FDA staff through FDA staff attendance at meetings of all major NCI decision-making and information exchange bodies concerning cytotoxic drugs -- including DN meetings, Phase I Working Group meetings, and New Drug Liaison meetings. It also provides that minutes of all of these meetings be sent to FDA. FDA staff attendance at the key NCI meetings is to keep them abreast of the progress of drug development, toxicity, and ADRs. In turn, a provision was made for a liaison NCI member to attend the FDA Oncologic Drugs Advisory Committee meetings.

Task Force Comment -

It is uniformly acknowledged that, in principle, the above mechanisms do establish a means for better understanding of NCI cytotoxic drug development problems by FDA, significantly improved routes of communication, and, therefore, a closer relationship with NCI than exists with industry. Reasons for this improved relationship between FDA and NCI as compared with industry are attributed to NCI being a "sister" federal agency and a nonprofit research program. The Task Force unequivocally considers improved communication between FDA and NCI to be a plus. Better scientific understanding by FDA staff of NCI's cytotoxic drug program can only benefit the regulatory actions which FDA must take, and understanding of FDA's regulatory role will help NCI reach its drug development goals; this can occur without compromising the regulatory role of FDA. Although there may be reasons for an arm's length relationship between FDA and industry, there is no reason for such distance between FDA and NCI.

The potential for the beneficial nature of these recently created channels of communication has not been fully met; in practice, the communication falls far short of that envisioned in principle (see the following section on Communication Problems).

C. Administrative Letters and Actions Regarding NCI Receive Higher Level Attention than Those for Industry

Administrative letters to the NCI dealing with important regulatory matters come from the level of the Director or the Associate Director for New Drug Evaluation, BD. For industry, such administrative letters regarding cytotoxic or other drugs are sent by the respective Division Directors. The following are paraphrased comments of various FDA staff concerning administrative letters and other actions:

- Letters to NCI are "nicer," and deal with NCI with a reasonableness and sensitivity that is better than industry.
- Letters to the NCI regarding deficiencies are sent in the same fashion as to industry. There is no difference in the manners in which FDA treats NCI and industry in this regard.
- Escalation of the level from which administrative letters are sent provides neither better function nor favoritism; it only provides the Bureau of Drugs with more information when it wants more information.
- "Hold" action to an NCI study must be approved and sent out by the Bureau of Drugs management level, whereas letters to industry are sent by division directors. This is management's prerogative. Few staff object to this.
- Clinical "holds" are ususally accomplished by team leaders within the Divisions; with NCI, this is not allowed unless the action goes up through Bureau Director level.
- BD is aware of some staff reviewer's vindictiveness and wants to protect NCI and to avoid a feud between FDA and NCI. In discussions, FDA medical officers say they are not vindictive, but are critical of NCI because of the prior quality of NCI's submissions.
- Ordinarily, inspection assignments are approved by the Division Director, but for sensitive issues (e.g., NCI) they have to be cleared at the higher levels in the Bureau of Drugs.
- If an investigation has "sensitivity" (e.g., inspections of public advisory committee member, of a federal agency,) the information escalates to higher Bureau levels. This is for information purposes, however, and no veto is exerted.

Task Force Comment -

It appears that some FDA staff at lower levels see the decision to approve letters to NCI at higher levels as having potential for "favoring" NCI or having lower level decisions reversed by higher levels. The Task Force believes that all IND sponsors should be dealt with in the same reasonable and sensitive fashion. That a routine administrative function needs to be selectively escalated to the BD Director level for action indicates an administrative defect or a management failure. If administrative letters are important enough or sensitive enough to require BD Director sign off, then they should be signed off at that level for all sponsors. If sign-off is an appropriate function of the Division Directors, they should be made fully responsible for accomplishing that role in a satisfactory fashion. If the division level staff is not performing to the satisfaction of the BD Director, appropriate steps should be taken to alter the manner of the Division's performance.

Recommendation -

The BD should define the appropriate level for sign-off responsibility for letters dealing with important regulatory matters and implement that decision consistently. The current inconsistency should be eliminated. Steps should be taken to ensure that division level personnel perform effectively and with reasonableness and sensitivity to all sponsors in accordance with BD policy.

D. Regulator to Regulatee Relationship of FDA and NCI

Broad general statements have been made regarding the unwillingness of NCI and the cancer investigator community to be regulated by FDA and of the unwillingness of FDA regulate vigorously to NCI. Samples of paraphrased comments by FDA staff follow:

- NCI objects to being investigated and has deliberately withheld documents.
- NCI does not feel obliged to respond to FDA requirements, and FDA does not force NCI to comply.
- When FDA tried to do directed investigations of NCI, FDA staff obtained good cooperation from NCI staff.
- FDA staff never have been told to keep hands off NCI. But there is an impression that FDA staff should not push too hard on a sister agency because we are all working together, and we are not out to embarrass a sister agency. There is an FDA staff perception at lower levels that maybe they would be hindered from doing regulatory follow-up on NCI matters.
- One FDA supervisor showed NCI all papers in relation to an investigation even though there was a potential criminal case being developed. This would not be done in a comparable situation with industry. Bureau Director staff writes to staff at lower levels to "treat NCI as everyone else" but then orally tells them to share information with NCI staff on the investigation.
- There is a feeling within FDA that the NCI cytotoxic drug system was set up above the division level, and whatever came to the master file should not be questioned. The FDA error was that FDA never objected to nor commented on the master file.
- NCI does not want to be regulated. NCI believes that FDA staff is not qualified to judge cytotoxic drugs.
- There is no operational distinction between FDA to NCI and FDA to industry relationships. There is no written or oral differentiation between the manners in which FDA regulates NCI and industry.

- There is no difference between the FDA relationships to NCI and to industry other than the escalation of administrative letter sign-off to the Bureau Director level.
- Oncology Division staff has never been told by Division or Bureau of Drugs level staff to go easy on NCI INDs.
- The cancer investigator community has favored moving NCI out from under the jurisdiction of the Food, Drug, and Cosmetic Act.
- NCI should not be treated differently from other sponsors scientifically, by policy, by principle, or administratively. NCI should not be exempt from FDA's regulations.
- The cancer community is arrogant, defensive to criticism, and does not want to be regulated.

Paraphrased comment from NCI staff -

- All NCI staff from the Director, NCI, down through lowest operational levels firmly believe that - (1) NCI cannot and should not become a regulatory agency; (2) FDA regulatory processes must be maintained; and (3) FDA should regulate NCI when NCI functions as a sponsor for INDs.
- The cancer investigator community sees NCI as a regulator.

Task Force Comment -

Apparently, many individual comments which have been made in the past have been interpreted by other individuals to reflect reluctance of NCI and the cancer investigator community to be regulated by FDA and reluctance of FDA to regulate NCI fully. It is clear that at the present time at the NCI and FDA policy levels there is no disagreement -- FDA must fulfill its regulatory responsibilities over NCI and NCI-supported investigators for the NCI INDs. No responsible party in either agency disagrees with this principle. In the course of normal operations, however, many conflicts and problems have arisen in which there were both substantive and procedural differences between members of the two agencies. Differing perspectives on intensity and purposes of monitoring, aggressiveness of regulatory action, differences in view as to both preclinical and clinical testing requirements, and other substantive issues have been legitimate bases for disagreements. Efforts of both agencies should focus on the substantive matters at hand; work toward resolution of important substantive problems; and establishment of better methods for each agency to exert its appropriate role -- NCI as the research organization sponsoring INDs for cytotoxic drugs and FDA as the appropriate regulating body. Mutual education and understanding of the respective research and regulatory roles of NCI and FDA would help both agencies perform their missions better.

E. Does FDA Accept Lower Quality Work from NCI than from Industry?

Allegations have been made that FDA is willing to accept lower quality work from NCI than it does from industry. Such comments have been made in a variety of areas. Although there is much overlap, an attempt will be made to describe the issues by considering the following questions:

1. Is FDA less demanding for toxicology data for cytotoxic drugs than for other rdugs? Of NCI than it is of Industry?

A sample of paraphrased FDA staff comments concerning the Toxicology is as follows:

- The new Toxicology Protocol is in conflict with 1968 Food, Drug, and Cosmetic Act standards. It does not meet the rigorous scientific requirements of that Act. Reviewers of INDs are forced to approve them on the basis of the Commissioner's approval of the new Toxicology Protocol, but such approvals are hedged with a limitation statement.
- In the absence of data organ monitoring needed in early human studies cannot be determined. Such decisions are based on animal toxicity findings. The decision to allow Phase I studies to be implemented prior to study of animal tissues is wrong. This wrong decision was made because it was made by oncologists and clinicians and not by toxicologists. The toxicologists were heard; they were not stifled, and staff will abide by the new Toxicology Protocol -- although it is thought to be wrong. In addition, cumulative toxicity will be missed with use of the new Protocol.
- To delay the submission of toxicology findings such as histopathology before beginning human studies is unnecessary.
- It is unsound to begin clinical studies without histopathology of animal work. The delay in onset of human studies of 2 to 4 months is all that would be necessary to have the data before starting. Industry sends in excess toxicity data.
- The Toxicology Protocol used too few animal toxicity studies. Animal studies are predictive of human toxicity. Two years ago, the NCI proposed using the mouse only but then moved back to including dog studies when pressured by FDA opinion.
- There are lesser toxicity requirements for cytotoxic drugs than for other drugs. However, this difference applies to industry sponsored cytotoxic drugs as well as those sponsored by NCI.

- Quality of NCI submissons is lower than can be justified by the use of the token toxicology (i.e., the new Toxicology Protocol) and restrictions and constraints imposed by the nature of cytotoxic drug investigation *per se*.

NCI Paraphrased Staff Comment -

- Prolonged survival provided by cytotoxic drug therapy (added to other modalities of treatment) now creates the possibility of development of chronic toxicity. Current studies are not adequate to identify long term toxicity; yet, treatment cannot be delayed because of the urgency of patients' problems. Therefore, new approaches need to be devised to study the potential chronic toxicity of this class of agents after introduction into widespread longterm use.

Task Force Comment -

The Task Force assessed in considerable detail the problems associated with the newly approved Toxicology Protocol. Although some defects have been identified (see Section V. Toxicology Protocol), the Task Force believes the claims that the new Toxicology Protocol have lowered the quality of preclinical toxicity testing are unfounded. The new Toxicology Protocol does use a different array of experimental animals and dosing schedules, but with a scheme that has been satisfactory in identifying a safe starting dose in humans. Analysis of available data indicates that animal toxicity is not predictive of major organ toxicity in humans; therefore, initial testing of patients in Phase I without animal histology (but with intensive general clinical monitoring) is not detrimental to such patients. Current animal testing by NCI constitutes an important and significant research effort to identify predictiveness of human toxicity. The need for methods for predicting cumulative and chronic toxicity has been recognized. The success of the new Toxicology Protocol in detecting cumulative toxicity needs to be assessed. Neither the present nor the previous Toxicology Protocol deals with problems of chronic toxicity, but FDA and NCI staff are considering what tests might be devised.

In summary, the different methods by which both NCI and FDA approach toxicology of cytotoxic drugs compared with all other drugs are scientifically sound and fully warranted in light of the nature of the patient problems to which the program is addressed and do not represent a compromise in quality. Further, there is no difference in the manner in which industry or NCI would be treated with regard to this class of drugs; all aspects of the Toxicology Protocol used by NCI could also be used by industry upon request.

2. Does FDA accept lower quality experimental protocols from NCI than from industry?

A sample of the perceptions of the quality of experimental protocols submitted by NCI for cytotoxic drug studies reveals widely divergent FDA views as follows in the paraphrased comments:

- NCI protocols are not scientifically adequate; they are biostatistically flawed.
- The quality of organization of IND data, presentation of data, and substance of submissions from NCI are not as good as those from industry.
- FDA staff rejects NCI INDs, but supervisors reverse judgments.
- NCI does not do Phase III studies. NCI investigators would rather work on new discoveries and neglect doing Phase III studies.
- DHAD protocols failed to acknowledge potential heart toxicity in 31 out of 33 protocols.
- Pharmacology data and IND quality from NCI are equal to that from industry.
- Industry uses between 10 and 12 patients for a Phase I study; FDA allows NCI to use up to 250 patients.
- Information in NCI INDs does not differ from that in INDs from industry.
- NCI studies are quite formally presented, well presented, and are not of lesser quality than industry submissions.
- Some Phase II studies are controlled, some are not. Historical controls have been downgraded in importance.
- The quality of NCI IND submissions is as good as that of industry's.
- Because of the condition of the cancer patients to whom cytotoxic drugs are given, the paucity of controlled experiments and relatively small numbers of patients are necessary; these obligatory characteristics of studies in such cancer patients constitute the "lower quality" referred to by others. The studies are not truly of lower quality, but rather are different; this is necessitated by the problems of the cancer patients. Industry and NCI cytotoxic drug INDs are of the same quality.

- In the past, NCI did not meet FDA standards for controlled clinical trials. Guidelines were subsequently developed, and NCI responded well.

- Industry never deviates from FDA suggestions, but NCI does. NCI fails to correct protocols that are found to have deficiencies and to educate investigators.

- FDA has not looked at the number of patients per individual tumor per individual drug; FDA feels it should not dictate the research plan to NCI, but does influence industry plans more.

- The cancer community does not use controlled trials enough, but instead, uses historical controls. They are looking for breakthroughs whose effects will be self-evident.

- FDA staff feels NCI cannot "control" the experiments proposed by investigators. NCI staff are in a weak position, leading commonly to protocol deficiencies.

Task Force Comment -

The comments about the quality of experimental clinical protocols submitted from NCI as compared with those from industry do not evidence a consensus. In any program as massive as the NCI cytotoxic drug development program there necessarily will be instances of less than high quality work. That some such instances have been identified is unequivocal. On the other hand, review by Task Force members of the various steps in the process of clinical protocol development and review revealed a detailed process which includes multiple layers of consideration by experienced program and investigator personnel that should ensure acceptable experimental and statistical design and generally sound submissions. The extent to which the small number of defective protocols identified may be representative of the program as a whole could not be addressed adequately within the scope of this Task Force effort. FDA staff accounts of individual instances of flaws in protocols do create concern; it would be desirable for NCI and FDA to pursue these for purposes of resolution of conflicting views and delineation of protocol design end-points that would satisfy both agencies.

Comments on the "quality of protocols" seem to be couched more in terms of comparison of cytotoxic drug protocols with those for other kinds of drugs. There are difficulties in creating ethical controlled clinical trials in a uniformly fatal disease, and there are restrictions on the number of patients to be studied because of the known drug toxicity. Ideal experimental design must be compromised to achieve the best possible patient care. As a result, many Phase II studies have used historial controls and Phase III studies, combination therapies. Thus, they may not be compared with experiments that can be performed in other kinds of illnesses. Beyond those limitations, however, the remaining tenets of sound experimental design should apply as in all drug trials.

3. Does FDA require from NCI submission of fewer data than from industry?

As a sponsor of cytotoxic drug INDs, NCI receives summary data rather than full individual case reports on the subjects participating in the Phases II and III clinical trials. NCI submissions to FDA are generally restricted to summary data. Comments have been made on the consequences of FDA requiring only summary data instead of raw data, to be submitted. Selected paraphrased FDA staff comments follow:

- Since the master file has been in operation, NCI stopped obtaining raw data. NCI gets only summary data which, in turn, is sent to FDA. There is no raw data data base to go back to for inspections. Therefore, the ability to audit data is markedly different in the NCI sponsored investigations than in those from industry.

- NCI submits abstracts and summary data while industry submits raw data in progress reports.

- FDA has not monitored NCI; there are no case reports to NCI.

- There is no difference in the kind of data submitted by NCI and industry. No raw data are requested in submissions relating to Phase I trials, Phase II trials, Phase III trials, or Group C status. Raw data are only required to be submitted as part of an NDA. Therefore, there is no evasion of requirements by NCI's use of summary data in these IND phases.

Task Force Comment -

The raw data (individual patient data) versus summary data problem has a convoluted origin. FDA does not require submission of raw data for Phases I, II, III, nor Group C drug status; the absence of raw data submissions by NCI in these phases of IND development, therefore, is not a technical deficiency. Some FDA staff are concerned that, since NCI does not have raw data, FDA staff cannot do on-site inspections at NCI because those inspections are based on auditing of raw data.

Further, routine field investigation assignments are derived from lists of investigators engaged mainly in NDA pivotal studies and from which NCI investigators largely are excluded because they do few such pivotal studies. The NCI lets the data it has accumulated be used by a pharmaceutical firm which submits the NDA, so again the NCI staff does not submit raw data to FDA. Further compounding this problem are NCI Group C status drugs which may for long periods of time have broad distribution to patients without reaching the NDA stage.

In summary, NCI submits few raw data to FDA as compared with industry; this is a byproduct of the fact that NCI does not take drug develop through the NDA phase, but may encourage the pharmaceutical firms to do so.

4. Does FDA require less chemical information and less evidence of agent purity from NCI than from industry?

Discrepant views have been offered about the extent to which the NCI-sponsored INDs are "approved" by FDA with less chemical information or evidence of a lower purity of product than would be true for INDs from industry or for INDs for other classes of drugs. Paraphrased comments made by FDA staff are as follows:

- Chemistry often is not available on NCI IND applications. There is a trend to go to the lowest common denominator of the information submitted. NCI uses a "reference substance" instead of "reference standard of high purity." Purity data are missing for most of the natural product INDs from NCI. There is less of a concern for the pharmacology and chemistry in these cytotoxic drugs submitted from NCI.
- NCI places a lower priority for studying the chemistry and purity of natural products than does industry.
- The supervisor has indicated that chemists have been over-reporting deficiencies for cytotoxic drugs.
- For some natural products in the NCI IND effort, there is no information as to the source of the materials, location of manufacturer, nature of manufacturing process, and similarity of multiple batches.
- All of the Oncology and Radiopharmaceutical Division chemical analysis staff are Ph.D.s with excellent credentials who together form a group much better than all of the other groups of chemists in the Office of New Drug Evaluation. Compromising the standards for judgment of the purity of compounds will result in these excellent people leaving.
- A number of hold recommendations for NCI INDs based on staff reviews indicating chemical deficiencies have been reversed by higher FDA authorities. This has led to a sense of futility and, therefore, the staff does not formally write out its objections as much as it would otherwise. Chemists are told that there are too many deficiencies, but not what those deficiencies are.
- Oncology and Radiopharmaceutical Division chemists are too finicky, and their judgments are overruled often. Management pushes for timely action not for compromise of quality of judgment.

- Supervisors have recommended retraction of IND holds' based on chemical deficiencies. It was believed that the items being asked for were essential later in the NDA process but that the available information was sufficient for the earlier phase studies. Some deficiency letters have been overruled directly. Some staff are satisfied with those actions, some are not. The number of chemistry deficiencies in the Oncology Division is an average 23.5 deficiencies per IND as compared with an average 7.0 deficiencies per IND from all other chemistry review groups in the drug reviewing divisions.
- One or two reviewers are tougher on NCI than they are on industry.
- BD has requests chemists in the Oncology Division to perform efficiently in a timely manner. The chemists have not been asked to compromise the quality of work.

Paraphrased NCI staff comment -

- Chemistry and purity submissions of NCI are of the highest quality. The purity of drugs proposed for Group C drugs fully satisfies requirements.

Task Force Comment -

The Task Force recognizes a controversy in the differing views between FDA staff and supervisors on the subject of chemical information and purity of the NCI-sponsored drugs. As in some other areas of controversy, staff at lower organizational levels indicate compromise of standards; staff at higher levels disagree. Regarding chemical information and purity of agents, the Task Force was not in a position to evaluate this controversy from a substantive point of view. The following concerns need to be separated:

1. Operationally, is there a lesser requirement for chemical information regarding natural product cytotoxic agents than for other agents at the time of introduction into early Phases I and II clinical testing?
2. If so, is it appropriate to allow early-phase testing of materials in humans with lesser information about agent purity (assuming that those compounds to be widely distributed will have their chemistries explored later)?
3. If the answer to Question 2 is yes, does in fact such further definition of chemistry information occur before a drug is assigned to Group C?
4. Finally, for cytotoxic agents with an NDA, is the chemical and purity information equal to that of other classes of drugs?

There has been no suggestion that there are differences in chemical information or purity testing in the INDs from NCI as compared with those of industry; rather, discrepancies described are between cytotoxic drugs and other drugs.

NCI and FDA staff should jointly analyze the characteristics of those chemical and purity reports on cytotoxic drugs thought to be less than adequate by some FDA staff for purposes of resolution of conflicting views and reaching agreement on the standards to be used.

5. Does FDA require less and accept tardy documentation supporting INDs from NCI as compared with industry?

Allegations have been made that the FDA requires less documentation and allows tardy submissions from NCI. Sample paraphrased FDA staff comments follow:

- Five NCI INDs were explored. There were many progress reports that wer absent and deficiency letters unanswered.
- Fifty percent of IND annual reports from NCI INDs were delinquent (except for the past year). Several INDs never had any annual reports.
- The INDs do not indicate the number of patients used in each phase of studies. An overall NCI synthesis of progress on individual drugs was absent. ADR reports were missing.
- NCI sends material to FDA that is tardy; this is practice, not policy.
- Many annual reports from NCI INDs are absent.
- Perceptions that NCI need not submit some supporting documents required of industry are simply not true.

Task Force Comment -

This allegation could not be assessed adequately by the Task Force. There were delinquency and tardiness of NCI reports prior to 1981. Since the beginning of 1981, the IDB record shows that annual reports have been submitted to FDA in a timely manner.

Recommendation -

For purposes of resolving conflicting views within FDA and improving communication between NCI and FDA, a study should be performed regarding - (1) the characteristics of clinical protocols thought to be flawed by some FDA staff (which should result in methods to ensure higher quality of future protocols implemented by the NCI cytotoxic drug development program); (2) the characteristics of those chemical and purity reports on cytotoxic drugs thought inadequate by some FDA staff (which should result in agreement on the standards to be used in subsequent INDs); and (3) allegations of FDA staff of frequent and extensive absence of documents required for various parts of the investigational new drug program. The Task Force suggests that the responsibility for this effort be given to an organization other than NCI or BD.

F. Does FDA Monitor NCI Less than It Monitors Industry?

A major concern has been the limited FDA monitoring of NCI INDs compared with industry. Unfortunately, "monitoring" is a term used frequently without discrimination between a wide range of activities -- at one end, data verification at the bedside or the laboratory bench for accuracy and completeness and, at the other, scientific program interim analyses of accumulating results. Discussions of these different kinds of "monitoring" have been provided in the Section VI, Clinical Trials.

Confounded with concerns for monitoring are concerns for "inspecting," an activity more toward the data verification end of the spectrum. Differing definitions have led to differing views about the extent to which FDA and NCI monitoring occurs. Selected paraphrased FDA staff comments follow:

- FDA tolerates poor management by NCI of the entire cytotoxic drug investigative program by not monitoring the number of patients administered a given cytotoxic drug for a given tumor. More patients are exposed than necessary to reach a scientific conclusion as to the usefulness of the drug. To expose excessive numbers of patients in this manner goes against the Nuremberg Code.

- Of a large number of routine investigations of investigators in the field, none has been performed on investigators of the NCI cytotoxic program. It is acknowledged that this is due to a surveillance strategy that focusses primarily on pivotal NDA studies, but such a strategy is unwise because it results in avoiding inspections of this important cytotoxic drug program.

- The explicit surveillance strategy that effectively omits NCI's cytotoxic drug investigators started 1 1/2 years ago; lack of inspection of the NCI investigators existed before that. If inspections of studies only supportive of NDAs (as opposed to those considered pivotal) were terminated, resources would be adequate to include the important IND efforts such as the NCI cytotoxic program.

- Once the determination is made by the Oncology Division as to what clinical investigators should have inspection site visits, that information is forwarded to supervisors, and then to the Bioresearch Monitoring Program. From then on, there is equal treatment by FDA of NCI and of industry.

- The NCI submissions to FDA may not contain the names of all investigators at cooperative study and satellite sites. These names are hard to get. One does not know what investigators are on what protocols.

- FDA does not inspect NCI because FDA management staff will not support those inspections and because of the MOU with NCI.

- FDA has not monitored NCI. There are no case reports at NCI and, therefore, inspections of raw data cannot occur.

- The surveillance strategy for use of investigative resources puts INDs third on the list. This is not a deliberate evasion of investigating NCI. Investigations occur by selecting investigator names at random; but the list does not include all NCI investigators. Principal investigators are on the list, but often not the many others who are in fact participating and performing studies. Why FDA has not corrected this is not known. Further, printouts of FDA name lists always contain many omissions.

- In practice, selection of whom is to be routinely inspected is made jointly by the Division of Scientific Investigations staff plus the Oncology Division staff.

- In a recent episode, the Division of Scientific Investigations sent a sponsor/monitor inspection to NCI rather than a for-cause clinical investigator inspection because of concern that BD management would stop a for-cause inspection.

- The subterfuge used regarding the FDA-initiated investigation of NCI was due to the pessimism the Division of Scientific Investigations staff has about getting approval for regulatory actions involving NCI. In part, things go more slowly with NCI matters because more people are involved in looking at them.

- The biggest problem is that NCI monitoring is less than in industry. Monitoring is a cost-effective management tool and is therefore used by industry. NCI should use that effective tool for broad program monitoring, auditing, and drug distribution. The research community pressures NCI not to monitor it. [The commentor was] not familiar with the CTMS.

- The proportion of routine investigations between NCI and industry is unknown [by the commentor]. The Oncology Division [commentor] has no role in selecting those to be investigated. Perhaps selection is done by BD management staff; this is not known.

- Industry is more studied than institutional sponsors (including NCI) because of the pivotal NDA studies priority. The number of NCI investigations was never analysed. The NCI monitoring scheme could be a reason to reduce FDA monitoring for overall efficient use of FDA resources. There is no policy to avoid monitoring NCI.

- Perceptions that NCI is not monitored are not true.

- FDA needs to monitor NCI data and investigations more. The Bureau of Drugs is considering changing its system for selecting field investigations to cover the NCI investigators. Five hundred fifty investigators were monitored in the last 4 years; the number of NCI cytotoxic drug therapy investigations was unknown and is not important enough to analyze.

- FDA inspectors spot check records of NCI investigators.

- FDA inspects NCI investigators for fraud and sloppy research less than other investigators.

- Peer review is not working as a quality assurance substitute for monitoring; repeated deficiencies regarding DHAD protocols indicate a failure to follow FDA deficiency letter recommendations.

- NCI is evolving in the direction of central control, but retaining investigator initiative. NCI is passive compared with industry's active control of investigators.

Paraphrased NCI staff comments follow:

- Since early 1980, NCI sponsored Phase I studies are monitored better than Phase II studies and are as well monitored as those of industry.

- Within cooperative groups, there are 640 active protocols; therefore, NCI cannot monitor tightly.

- NCI relies on peer review for selection of excellent, responsible, experienced investigators to avoid fraud and sloppy research. Also, NCI uses outside contract monitors for Phase I and Phase II studies.

- Self monitoring by cooperative study groups is extensive and effective.

- Phase I and Phase II monitoring is necessary because of the great reliance placed on human studies for determining toxicity. Extension of monitoring to all NIH studies is not advisable.

Task Force Comment -

The Task Force's views on the monitoring problem have been presented in discussions of the Section V, Toxicology Protocol, and Section VI, Clinical Trials. Clearly, there are some differences in the way FDA monitors NCI as compared with industry. More important is whether those differences are appropriate. Observations on these differences are summarized briefly as follows:

1. The character of preclinical toxicity testing differences is due to differences between the class of cytotoxic drugs and other drugs and not due to a difference between the FDA approach to NCI and to industry. Once the rationale for the Toxicology Protocol is evaluated and accepted, there should be no significant problems requiring resolution.

2. "Monitoring" encompasses both "data verification" and "scientific program interim analysis." Figure 4 in Section VI summarizes the complex nature of the monitoring by NCI and by FDA of the cytotoxic program components. In the past, industry did much more data verification than did NCI. Recently, NCI has instituted a vigorous data verification and interim analysis process for its highly and closely controlled Phase I and early Phase II contractual studies which equals or exceeds that of industry. Data verification efforts exist internal to some Phase III cooperative group studies. For all the phases, NCI does extensive interim analyses; suggestions for further improvements in the interim analysis process were made in Section VI, Clinical Trials.

   FDA engages in little data verification of the NCI cytotoxic drug program, either directly or via NCI. This contrasts with the considerable data verification effort of FDA directed toward industry generally occurring through "routine" inspections of investigators' data. However, because of the inspection program surveillance strategy which gives cytotoxic drug IND studies low priority, industry is treated the same as is NCI regarding data verification for this class of drugs.

   FDA performs an oversight function on NCI's interim analysis processes via review of NCI's submitted annual reports, clinical protocols, and minutes of Working Groups and cooperative study groups. There has not been any evidence presented that FDA's overview of the NCI interim analysis process is less than that for industry's cytotoxic drug efforts; indeed, the extra communication channels established between NCI and FDA probably give FDA opportunity for greater oversight of NCI than of industry cytotoxic drug interim analyses.

3. Drug distribution and control of cytotoxic drugs has progressively improved. A drug distribution system being implemented by NCI will meet monitoring needs of both NCI and FDA and likely will equal those of industry.

The above is a synopsis of the Task Force views on the monitoring problem. Some small differences do exist between the manners in which FDA monitors NCI and industry, but these differences are not inappropriate. Improvements are needed in some areas. Many of the complaints and counter-complaints about monitoring appear minor compared with the importance of the overall issues; the Task Force believes that if the substantive issues are considered and addressed seriously, the NCI cytotoxic drug development program can be made more effective and efficient while allowing FDA to fulfill its regulatory role. The Task Force has not discerned a pervasive or significant policy of "favoring" NCI as compared with industry by imposing fewer monitoring requirements upon NCI.

G. Unique Character of NCI's Group C Drugs

Group C status (described in Section VII, Investigational New Drug Distribution and Investigators) is conferred upon cytotoxic drugs by joint decision of NCI and FDA advisory bodies. There has been controversy about the appropriateness of using the Group C mechanism to effect broad distribution to cancer patients. FDA staff paraphrased comments follow:

- Group C status is used by NCI to bypass safeguards offered by the NDA process. Group C drugs are approved by FDA with lesser scientific rigor. This is the only means by which a drug may reach broad distribution without approval of an NDA.
- The Supreme Court has ruled that the criteria by which FDA must judge a drug for broad distribution (marketing) are: (1) prolonged survival, (2) improved quality of life, and (3) reduced pain and suffering. Use of other standards bypasses the protection of the Food, Drug, and Cosmetic Act.
- Raw data are submitted by industry before widespread distribution as a marketed drug can occur. In contrast, only summary data are submitted by NCI; therefore, widespread distribution as a Group C drug occurs without submission and review of raw data.
- Group C status is conferred on a drug only after approval by the NCI Board of Scientific Counselors, submission to FDA, and approval by the FDA Oncologic Drugs Advisory Committee (the same body that passes on NDAs). Group C status itself is unique for the class of cytotoxic drugs and can be used by industry as well as NCI.
- Group C status is not unique to NCI. A pharmaceutical firm has been granted Group C status for a drug to be distributed by it. The NCI Group C program is unique by virtue of its size. It is an extensive program that approaches being a small medical care delivery system.
- Poorer reference standards are used for drugs in Group C status than for drugs reaching NDA approval. Supervisors have overruled deficiency judgments of staff.
- Review of Group C drugs by the FDA is scientifically rigorous.
- It is not realistic to attempt to spell out in detail safety and efficacy criteria in regulations for NDA and Drug C approval. FDA is not locked into rigid requirements for NDA approval.

- Data on prolongation of life span are desirable for NDA approval. Remission rates are also useful. Criteria for Group C and NDA approval are not so different.
- NCI is developing a holistic care approach, not NDA oriented. It is self-contained medical care system.

NCI paraphrased staff comments -

- The focus of NCI interest in the early testing phases is on a drug; later it shifts to the use of that drug in modifying treatment for a given cancer. In contrast, industry will focus on the NDA process and the support of studies to obtain market approval for the a narrow use. NCI has progressively increased its attempt to support studies which will eventually be useful to support NDA approval by FDA.
- FDA uses the criteria of prolonged survival, improved quality of life, and reduced pain and suffering as criteria for approval of NDAs. NCI believes that response of the cancer to drugs is an additional criterion which should be used; responses may be a significant change in tumor size, reduction of white blood counts, palliation, increased ambulation, and comfort. A significant response rate to an experimental cytotoxic drug will often indicate that the drug will in fact alter the clinical pattern of treatment of a cancer when it is added to other modalities of therapy. FDA will not accept studies as supporting an NDA in which there is confounding of treatment results with other drug treatments. Therefore, broader distribution of Group C status drugs allows those drugs which have been demonstrated to be clinically useful to reach a larger number of patients while awaiting further studies that would satisfy NDA approval requirements. This "response rate" criterion and its relationship to approval of drugs for marketing via the NDA process pose an important scientific problem for the entire oncologic community.
- Information on chemistry and purity of Group C drugs matches that of other drugs and of industry.
- There is no difference between safety and efficacy of Group C drugs and NDA approved drugs.
- NCI is motivated to cure cancer. That requires using multiple drugs. NCI is not directed to single drug studies.
- NCI hopes to get FDA to accept multiple-drug trials as NDA supporting studies when large changes in results occur. There is no need to change FDA regulations.

Task Force Comment -

The establishment of a Group C status for the cytotoxic drug program of NCI is not unique and does not represent treating NCI differently from industry. Industry has used the Group C mechanism, though infrequently. The Task Force sees Group C status as using different standards for allowing a drug to reach broad (but controlled) distributions than for an NDA-approved drug. Some FDA staff have less confidence in data that have not been verified by the field inspection process as is required for NDA approval. There is a compensatory control provided by the Group C drugs only to qualified physicians for use only on specified tumors. The Task Force believes that Group C status is an appropriate method for bringing important medications to patients who need them. The controversy as to whether or not FDA is "favoring" NCI by its attitude about Group C status pales by comparison with the importance of the underlying issues. What is important is making as explicit as possible the criteria for broad distribution of cytotoxic drugs. FDA has criteria for Group C status used by its Oncologic Drugs Advisory Committee.

XIII. COMMUNICATION PROBLEMS

Communication problems underlie a number of the difficulties with the NCI/FDA handling of the cytotoxic drug program. There is need for mutual respect for differences of opinion between the two agencies' staff and serious exploration of the important substantive problems about which differing views are held.

Incomplete and unsatisfactory communication may result from inadequate resources with which to address the responsibilities of given program staff. Observations about negative aspects of performance and communication must be tempered by recognition that some of the difficulty results from an imbalance between the size of FDA and NCI staff and the extremely large cytotoxic drug program.

Many of the perceived substantive problems discussed previously in this report could be remedied by better communication. Many areas of divergent views within the agencies reflect poor or incomplete communication. The extent of efforts to overcome communication barriers was difficult to discern. Increased effort at improved communication will assist in resolution of some but not all problems. When full, thorough, honest, and open deliberation has occurred and differences of view remain, further communication efforts simply may aggravate the discomfort and tension of those disagreeing. In science and medicine differing opinions are inevitable and desirable. Continuous effort must be made to evolve the best system of ideas for understanding the science and medicine of therapeutic agents. In a community of scholars, it is the responsibility of each to express forthrightly views held and the rationale for them.

FDA, as a regulatory body, must assemble its single "agency view" on given issues so as to avoid confusing sponsors who must meet FDA requirements. In most instances, differences of view between staff are easily accommodated; they simply exist. On occasion, differences of view are held on matters considered so important as to preclude continued mutual acceptance of those opposing views. Ultimately, an operational resolution must be made.

The individual suggesting change will find acceptance of the recommended change or must accept the absence of change. For what are believed to be critically important issues, the failure to effect institutional change may result in some instances of a request for transfer to another position or a resignation in protest. On the other hand, prolonged and severe refusal to accept rejections of proposed change can be ignored or, if it impedes the functioning of the institution, can result in involuntary transfer or separation. It is important to reach an appropriate balance between intellectual and academic freedom to express divergent ideas and the need for an organizational coherence of an agency's policies and positions.

Communication problems will be discussed in this section in relation to many of the issues covered in the immediately preceding section. In the following, the letters and numerals correspond to those used in the preceding section on "Comparison of FDA-NCI Relationships with FDA-Industry Relationships."

Paraphrased comments of persons interviewed are set off and indicated with a different type style.

A. Pre-1975 History - Not relevant to communication problem discussion.

B. Channels Established to Increase the Communication Between FDA and NCI

The establishment of communication channels, such as joint meetings, the NCI DMF, and the MOU was strongly endorsed as being supportive of both NCI research goals and FDA regulatory functions.

Paraphrased comments on these channels of communication from FDA staff follow:

- Indicine-N-Oxide liver toxicity was known by NCI, reported by NCI to investigators, but not noted in the IND. FDA knew about it, but only via an unofficial communication. The information from Phase I Working Groups and New Drug Liaison meetings are not formally transmitted to the FDA. Group leaders usually do not attend those meetings, so minutes are sent to whomever does attend. The content of those minutes is so superb that it would correct all of the qualitative deficiency of NCI INDs if they became part of the IND.
- NCI staff tried to force regulatory decisions from FDA staff members at the NCI meetings to which they were invited.
- There is poor communication between NCI and FDA staff.
- Staff stopped going to NCI meetings 1 year ago because (a) FDA staff was functioning in a regulatory role, not in a scientific one; (b) the information at those meetings was mainly oral, and regulatory actions require written material; (c) the meetings were used as informal means of notifying FDA instead of the more formal written means which are required; and (d) NCI staff asks FDA staff how to deal with specific problems, which puts FDA staff members in a position of being unable to respond on the spot as regulators.
- There is bad blood between staff at the various NCI levels; staff at lower organizational levels are ordered by higher level staff.
- There is a deliberate game to delay histology data delivery by NCI to FDA.
- There are no data upon which to base the 9 percent Phase I therapeutic response which NCI claims.
- NCI staff have been told not to present data to FDA because it would be misunderstood.
- NCI staff need their jobs and, therefore, have to be careful of what is said at meetings.
- Some FDA staff think of NCI investigators as arrogant, in an invory tower, and who need to have their errors surfaced; some NCI staff see FDA staff as police and poor scientists. This is less true today than in the past.

- Several FDA staff members have expressed a belief that it is not appropriate for FDA to be formally represented at NCI staff meetings because (a) FDA does not attend working meetings on industrially developed drugs; (b) concern that NCI will not formally submit material if FDA is made aware of it at meetings; (c) the presence of FDA staff may be inhibitory to open discussion among the investigators; and (d) FDA representatives have been asked to give a regulatory opinion on the basis of a slide show rather than a complete, documented submission and full review.

- Statements or actions suggesting special treatment of NCI have occurred, such as (a) avoiding confrontation with sister agencies, (b) friendly calls to sister agency prior to inspection visits, (c) sharing information regarding inspections, and (d) the protracted time course and elevated level of review of documents issuing after inspection of a sister agency. When viewed separately there are obviously no improprieties, and certainly supervisory review is the proper prerogative of management. The overall effect does engender, however, the perception of special treatment of sister agencies.

Paraphrased NCI staff comments -

- Interaction between FDA and NCI is less than ideal despite efforts. ADR feedback from FDA is negligible. Phase I and Phase II and Decision Network meetings to which FDA staff are invited are rarely attended by FDA staff.

- NCI is willing to submit any paper it has that FDA wants.

- Communication problems exist at the Division Director level. Communication between NCI and FDA is less than desirable. Most communication is formal and written. All phone calls to FDA from NCI become memos for the record which makes NCI staff leery.

- Congressional hearings were the first time at which NCI heard about a series of FDA complaints about NCI INDs.

- Interaction of FDA and NCI should be more on a scientist to scientist basis; then the frictions will end.

Task Force Comment -

The channels of communication between FDA and NCI constructed over the past few years have been excellent in principle. In practice, they have fallen short of expectations and potential. Comments from some FDA and NCI staff acknowledge that on a day-to-day basis these channels of communication do not operate at a satisfactory level. The deliberate structure for interaction should have provided the opportunity for FDA staff to indicate easily what information it needed from NCI and, in turn, for NCI to respond. In part, the flaws in communication have resulted from a failure to distinguish clearly and explicitly between scientific discussions and regulatory actions; and between formal and informal communications. The respective roles of NCI and FDA staff in these joint activities should be delineated. Specifically, Working Group and DN meetings should be scientific sessions at which there should be free expression of ideas, discussion, and programmatic decision-making by NCI. FDA staff can participate as scientist colleagues, but they should not make any regulatory judgments at those meetings. NCI should select appropriate substantive information covered at such meetings (including minutes) and formally submit it in writing to the respective specific IND record at FDA. Questions as to regulatory issues should be formally addressed and responded to in writing. Clear separation of the scientific discussions from the regulatory roles will allow staff from both agencies to appreciate better both the substantive and the administrative components of their respective agency's functions and actions.

Recommendation -

NCI meetings should be structured for free interchange of ideas on the science and medicine of cytotoxic drugs while insulating those discussions from FDA regulatory functions of attending FDA staff. Relevant information from such meetings should be submitted formally from NCI to specific FDA IND files. Regulatory issues should be addressed formally in writing, and responded to in writing. The FDA and NCI communication channels should be used fully.

C. Escalation of Administrative Letters and Actions Regarding NCI to Higher FDA Levels

The escalation of administrative letters to NCI to the Office of the Director, BD, has been associated with a failure of communication or understanding by some levels of FDA staff. The Task Force is not in favor of this selective escalation (see Recommendation, Section XII). Free and open comprehensive discussions of the issues should have clarified the reasons underlying the decision to escalate such administrative letters. If unacceptable performance of some BD staff was the reason for the decision, discussions should provide opportunity for resolution of underlying problems.

D. Regulatory-Regulatee Relationships of FDA and NCI

At all levels of FDA and NCI, staff agree that FDA must fulfill its regulatory responsibilities toward NCI as a sponsor for cytotoxic drugs. Differing perspectives on intensity of monitoring needed, aggressiveness of regulatory action, preclinical and clinical testing requirements, and other substantive issues have been the bases for disagreements between the two agencies. Improved communication should assist in resolution of these conflicts on substantive issues and thereby remove concern about the regulator-regulatee relationships between FDA and NCI. Individual passing comments made in course of disagreement on substantive matters, often by busy staff, have been misinterpreted as an NCI institutional position against being regulated by FDA. Some NCI staff may not like the regulatory role of FDA, but do say it is needed and that they will attempt to abide by the rules.

E. Acceptance of Lower Quality Work from NCI

1. Toxicology Data

Concerns about lesser toxicity requirements for cytotoxic than for other drugs stem from different scientific interpretations of available data. Endorsement of the Toxicology Protocol by both NCI and FDA is appropriate in the light of current knowledge. Extensive open deliberations were used to arrive at the decision to accept the Toxicology Protocol. Strong objections to the Protocol persist within BD divisions. Resolution of these different views is assisted by obtaining new data and refining decisions on acceptability of risks; full and open communication and repeated examinations of the problem will be helpful.

2. Experimental Protocols

The obligatory characteristics of having less ideally controlled experiments in cancer drug trials is construed by some staff to make these "lower quality studies." The NCI process for supporting clinical studies is good, and the quality of studies is appropriate considering the constraints imposed by the cancer problem. Improved communications between NCI and FDA staff could help identify and improve those instances of flawed clinical protocols and improve the joint effort of both agencies to make available to cancer patients effective and safe treatment modalities.

3. Requirement for Fewer Data

Confusion of "fewer data" and "raw data" has served as a proxy for an indirectly related problem. Because NCI does not submit NDAs, and since raw data are required by FDA only for NDAs, NCI submits fewer raw data to FDA than does industry. Because FDA selects investigators to undergo routine investigations mainly from those doing NDA-directed studies, FDA has done little monitoring of NCI investigators.

Submissions with fewer raw data have been equated to poor quality submissions; this semantic confusion could have been avoided by better communication. The concern for not excluding NCI researchers from inspections also could have been addressed directly earlier. Recently, BD has considered changing its surveillance pattern for inspection efforts so that NCI investigators will be more likely to be included.

4. Less Chemical Information and Purity Requirements

There is disagreement about (a) which Phase I studies can proceed with lesser chemistry information and purity requirements; (b) the need for later increases in purity for compounds which are more broadly distributed (NDA drugs or Group C drugs); and (c) standards for the chemistry judgments being made routinely. It is appropriate to avoid the great costs of doing definitive studies before it is known whether or not a drug will be dropped from study early. Differences in view between some FDA and some NCI staff suggest that there is need for communication to resolve these issues.

F. FDA Monitoring of NCI

"Monitoring" is a term used frequently without careful discrimination between the subsets of activities encompassed. Perceived differences in views about the degree of monitoring of NCI trials result in part from different uses of the term. Detailed analysis of monitoring (both data verification and interim analysis) of cytotoxic drug programs reveals no reduced monitoring of NCI as compared with monitoring of industry (see Section VI). Differences of monitoring between cytotoxic and other classes of drugs have been identified. Open discussion of monitoring data can clarify the FDA stance toward NCI and resolve disagreements about the degree of monitoring needed.

Summary

The critical substantive issues of cytotoxic drug development and procedural matters for resolution of program problems are of great importance to the health and welfare of the public. Communication problems contribute to some of the difficulties with the NCI/FDA handling of the cytotoxic drug program and warrant major efforts within and between the agencies to resolve differences. While retaining tolerance for expression of differing views, movement must be made toward organizational coherence of agency policies necessary for the institutional performance of missions.

Differences of view among FDA BD staff on important issues underlying FDA's regulatory functions have been strong and long standing, have diverted important resources from performing these functions, and have clouded FDA's formal positions.

Bureau of Drugs Management

In addition to description of poor communication between and within FDA and NCI, the Task Force heard a number of individual allegations regarding personnel problems, low morale, and inefficient managerial practices of the FDA BD divisions and BD management dealing with cytotoxic drugs.

The Task Force lacked the time to assess the merit of many of these allegations. Even if proved in some instances, they may reflect problems that may realistically be difficult to solve.

Recommendation -

In view of the allegations, the Office of the Assistant Secretary of Health's Office of Management should undertake a management study of the BD divisions and BD managers dealing with cytotoxic drugs to examine areas about which questions have been raised, such as organization, personnel and staffing, budget, decision-making procedures, internal communications, morale, workload, filing system, and paperflow.

XIV. SANCTIONS

During the course of its deliberations the Task Force considered the sanctions available to NCI and FDA for dealing with violations of their respective rules and procedures. In the time available, the Task Force was able to collate the following information based upon existing expertise on the Task Force itself or immediately available to it.

National Cancer Institute

1. NCI's primary forms of leverage in dealing with institutions and investigators involve control over funding, 1/ control over participation in NCI sponsored trials, and control over access to NCI distributed drugs.

2. The principal mechanism most commonly used by NCI, and the rest of NIH, for dealing with wrongdoing is denial or withdrawal of funding.

In exercising its discretionary authority to award a research grant, NCI is required under the PHS Research Project Grant Regulations to take into account the "competency of the proposed staff" (42 CFR 52.5). In addition, NCI may take into account such other pertinent factors as the "fiscal and administrative capabilities" of the applicant [45 CFR 76.1(c)] and, when appropriate, whether the applicant institution and its key personnel have in the past adequately discharged their responsibilities for protection of human subjects [45 CFR 46.123(b)].

When improper conduct comes to light after a grant has been awarded, the HHS Grants Administration Regulations authorize NCI to suspend or terminate the grant if the conduct constitutes a material failure to comply with the terms of that grant (45 CFR 74.114, 74.115). As currently worded, this authority to suspend or terminate does not clearly refer to conduct not related to the particular grant in question. However, since essentially all grants are made to institutions, rather than

---

1/ The discussion which follows will deal only with funding through assistance mechanisms (e.g., grants). However, although the legal citations, phrasing, and some details may be different for contracts, what is said about assistance in the discussion is largely true for contracts as well.

individuals, when NCI and a grantee institution agree that an investigator on the grant has engaged in improper conduct in any context, they can take action to terminate the grant by mutual consent without regard to the wishes of the investigator. 2/

As an alternative to dealing with applications from wrongdoers on a case-by-case basis, NCI may recommend that debarment proceedings be undertaken against an institution or an investigator (45 CFR Part 76). Under regulations which became effective in November 1980, the Secretary of HHS may take steps in accordance with formal procedures set forth in the regulations to render a wrongdoer ineligible for grant support. If an institution or individual is debarred, NCI may not even consider applications for research support from the institution.

3. Additionally, under HHS regulations (45 CFR 46.103) an institution must have an approved assurance before it may engage in HHS funded research involving human subjects. If an institution repeatedly failed to live up to its assurance, HHS could in theory withdraw its approval. As far as the Task Force can determine, such a step has never in fact been taken, however.

4. Apart from funding controls, as with any IND sponsor, NCI has discretionary authority to decide which investigators it wishes to use in its drug trials. In accordance with 21 CFR 312.1(a)(13), NCI must obtain a form FD 1573 from each investigator involved in a study.

5. NCI also has discretionary authority under 42 U.S.C. 241 and 285 to distribute drugs and other substances to researchers, but may refuse to distribute to individual scientists when there is a reasonable basis for such refusal.

6. Finally, depending on the circumstances, particular instances of wrongdoing in connection with NCI awards could violate federal criminal laws [for example: 18 U.S.C. 286 (conspiracy to defraud the Government), 287 (false claims),

---

2/ Alternatively, with NCI approval, the institution may replace the investigator or undertake some other corrective action (such as imposing added administrative controls on the investigator).

and 1001 (false statements)], the Federal Food, Drug, and Cosmetic Act, and laws relating to particular controlled substances. Any decision whether or not to prosecute a wrongdoer, however, would be made by appropriate law enforcement authorities (e.g., the Justice Department), rather than NCI.

Food and Drug Administration

1. As primarily a regulatory agency, FDA's principal sanction for dealing with violators of FDA's investigational new drug regulations is to withdraw the exemption that permits an organization or investigator to carry out clinical studies using new drugs, without having first to go through the process of submitting an NDA and having it approved. Short of imposing any sanction, FDA also has established procedures for advising investigators of deficiencies which, if not corrected, could lead to sanctions.

2. Dealing more specifically with the sanctions, under applicable FDA regulations [21 CFR 312(c), Part 16] a clinical investigator who fails to carry out FDA's investigational new drug requirements may be disqualified as an acceptable researcher to conduct clinical investigations under the exemption previously referred to (i.e., Notice of Claimed Exemption for a New Drug, or IND).

If an investigator is disqualified through the procedures set forth in the regulations, his or her name is placed on a list of disqualified clinical investigators that is available to the public upon request. In addition, FDA notifies sponsors of its action and directs them to reexamine studies that relied, wholly or partly, on the investigator's data to determine whether or not elimination of the data is likely to invalidate the study. If FDA decides that, after elimination of this data, the remaining data fail to support the conclusion that it is reasonably safe to continue the study, FDA will terminate the exemption in accordance with applicable procedures and the study may not be used to support an NDA.

3. As against the sponsor, FDA regulations [21 CFR 312.1 (a)(2)] allow FDA 30 days within which to place a "hold" on an IND for the purpose of withholding or restricting the use of a drug in humans. The regulations [21 CFR 312(d), Part 16] further provide for termination of an IND if FDA finds that one or more specified deficiencies exist and the sponsor's explanation or proposed corrective action is not accepted by FDA. The types of deficiencies that may lead to such action are as follows:

"(1) The submitted 'Notice of claimed investigational exemption for a new drug' contains an untrue statement of a material fact or omits material information required by said notice; or

(2) The results of prior investigations made with the drug are inadequate to support a conclusion that it is reasonably safe to initiate or continue the intended clinical investigations with the drug; or

(3) There is substantial evidence to show that the drug is unsafe for the purposes and in the manner for which it is offered for investigational use; or

(4) There is convincing evidence that the drug is ineffective for the purposes for which it is offered for investigational use; or

(5) The methods, facilities, and controls used for the manufacturing, processing, and packing of the investigational drug are inadequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug; or

(6) The plan for clinical investigations of the drugs described under section 10 of the 'Notice of claimed investigational exemption for a new drug' is not a reasonable plan in whole or in part, solely for a bona fide scientific investigation to determine whether or not the drug is safe and effective for use; or

(7) The clinical investigations are not being conducted in accordance with the plan submitted in the 'Notice of claimed investigational exemption for a new drug'; or

(8) The drug is not intended solely for investigational use, since it is being or is to be sold or otherwise distributed for commercial purposes not justified by the requirements of the investigation; or

(9) The labeling or other informational material submitted for the drug as required by section 7 of the 'Notice of claimed investigational exemption for a new drug' or any other labeling of the drug disseminated within the United States by or on behalf of the sponsor fails to contain an accurate description of prior investigations or experience and their results pertinent

to the safety and possible usefulness of the drug, including all relevant hazards, contraindications, side-effects, and precautions; or any promotional materials disseminated within the United States by or on behalf of the sponsor contains any representation or suggestion that the drug is safe or that its usefulness has been established for the purposes for which it is offered for investigations; or

(10) The sponsor fails to submit accurate reports of the progress of the investigations with significant findings at intervals not exceeding 1 year; or

(11) The clinical investigations are not being conducted in compliance with the requirements regarding institutional review set forth in this part or in Part 56 of this chapter, or informed consent set forth in Part 50 of this chapter; or

(12) All nonclinical laboratory studies were not conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if such studies were not conducted in compliance with such regulations, all differences between the practices used in conducting the study and the good laboratory practice regulations were not described in detail; or

(13) The sponsor fails promptly to investigate and inform the Food and Drug Administration and all investigators of newly found serious or potentially serious hazards, contraindications, side-effects, and precautions pertinent to the safety of the new drug."

4. Under its recently adopted regulations relating to IRBs, FDA may take administrative action, including disqualification, against an IRB or its parent institution for failure to comply with those regulations (21 CFR 56.120, 56.121, Part 16).

5. FDA also has authority to obtain court injunctions against further violations of the Food, Drug, and Cosmetic Act and its regulations and to seize unapproved new drugs.

6. As in the case of NCI, under some circumstances, particular instances of wrongdoing could constitute violations of Federal criminal laws and be punishable under those laws.

Mechanisms for Keeping Concerned Parties Informed

1. As has already been indicated, once FDA disqualifies a clinical investigator, this information would be available to a member of the public upon request.

In addition, the Task Force was advised that FDA informally advises appropriate NIH offices of investigators who have been disqualified.

2. Although no one has yet been debarred from eligibility for assistance, under the new HHS debarment regulations referred to above, if this were to occur a notice informing the public would be published in the Federal Register.

3. Regarding ongoing investigations of alleged improper conduct affecting both NCI and FDA, the Task Force was advised of particular instances in which NCI (or NIH) and FDA shared information, but there appears to be no standard procedure for doing so.

NIH has a new internal alert procedure for seeing to it that affected NIH personnel are aware of ongoing investigations, on a need-to-know basis. As presently constituted, the alert procedure provides a way for NIH to track incoming grant applications and contract proposals from individuals and institutions under investigation by NIH or other Government units. The procedure is not intended to block issuance of an award, but rather to provide an orderly process for responsible NIH staff to consider relevant investigative findings prior to making an award. (See Appendix G for an explanation of the NIH Alert System).

4. In two recent cases, NIH has decided to advise NIH advisory bodies responsible for reviewing funding applications from specific investigators of prior improper conduct by these investigators.

Frequency of Sanctions

A. FDA

Since 1964, FDA has disqualified 43 clinical investigators under its IND regulations. Of these, six have been reinstated and are again eligible to use INDs. During the last 4 years eight cases involving investigators were referred to the Justice Department for prosecution, and, in four cases the Government obtained convictions. (Two of the eight cases are still pending).

In fiscal year 1981, FDA received about 1150 INDs. Of these 183 were put on "hold" based on concerns about the reasonable safety of the drug. In the same year, a total of 27 IND exemptions were terminated because of failure by the sponsor to comply with applicable requirements. There are now roughly 6,000 active INDs.

In addition to these more formal proceedings, each year FDA conducts several hundred inspections of sponsors, investigators, and IRBs. In most cases, deficiencies are resolved through negotiation, but in a small percentage of cases, more official communication and/or action is required.

B. NCI/NIH

In considering the question of use of sanctions, the Task Force considered NIH as a whole, of which NCI is just a part. NIH is not a regulatory agency and, in contrast to FDA, it does not have a large staff of inspectors. It relies for the most part on peer review and normal program monitoring by NIH staff and by the grantee institutions themselves to uncover problems with particular researchers. When human subjects are involved, such as in clinical studies, it also relies on the IRBs to see that subjects are protected.

In the past, when investigators have acted improperly NIH has worked with the grantee institution to resolve the problem--for example, through termination of the project by voluntary agreement, substitution of a new investigator, or imposition of added administrative controls on the investigator. In only a very few cases has a grant ever had to be suspended or terminated for cause through unilateral NIH action.

The debarment regulations, referred to above, have only recently been made final. No one has yet been debarred under them. 3/

Comment

Judicious use of sanctions in appropriate cases serves several important purposes. Not only does it punish the wrongdoer, but it also (1) serves as a reminder to others of the requirements

---

3/ Nor has anyone ever been debarred under similar HHS regulations which have been applicable to contracts for many years.

that were transgressed; (2) underscores the importance the agency places on these requirements; and (3) may deter potential wrongdoers.

The problems encountered with the NCI drug development program are not primarily the result of the existence or absence of sanctions. Both NCI and FDA have significant steps each can take against wrongdoers if they choose to do so.

It is unfair to impose sanctions if the rules allegedly violated are unclear, however. For example, investigators are required by form FD 1573 to report "any emergent problems, serious adverse reactions, or proposed procedural changes which may affect the status of the investigation." Such a definition leaves a great deal to the judgment of investigators as to what to report, particularly in the case of subjects who are already seriously ill before entering the research. Further guidance may be needed so there is an adequate standard against which investigator-reporting can be measured.

Nevertheless, when clear and straightforward violations of NCI or FDA requirements occur, appropriate action should be taken against wrongdoers, as follows:

Recommendations

1. NCI should more actively impose sanctions against wrongdoers.

2. NCI management officials should be reminded of their obligations to report violations of federal rules and regulations to appropriate law enforcement authorities, e.g., HHS Inspector General.

3. Sanctions should be considered against the institution as well as the individual wrongdoer when multiple violations occur at a single institution, when appropriate.

4. 45 CFR Part 74 should be amended to allow suspension or termination of a grant, not only for causes related to that grant, but for causes related to activities of the investigator in other contexts.

5. The Director, NIH, should review the NCI procedures for denying investigators use of NCI-sponsored drugs for clinical investigations to ensure that the procedures are fair and to provide for consistent treatment of investigators.

6. FDA and NIH should expedite development of plans and procedures for the sharing of information regarding ongoing and completed regulatory and monitoring investigations including the sharing of findings of wrongdoing with agencies and organizations (federal and nonfederal) outside HHS.

The Task Force suggests, on the basis of limited information, that the main gap in this area relates to coordination of efforts and sharing of information regarding potential wrongdoing.

XV. SUMMARY

NCI's anticancer drug development program is a complex, unique scientific and therapeutic endeavor focussed on one facet of cancer research and treatment while FDA's BD has the role of regulating NCI's new drug development to ensure that unacceptably dangerous drugs are not used in the treatment of cancer in humans. These two agencies operate on the frontier of science and medicine to develop chemotherapy for more than 100 forms of cancer.

The Task Force assumed its charge with recognition of the pressure on NCI to succeed in the development of new drugs and the necessity that FDA ensure the timely approval of safe and effective new drugs. Against this background, and its deliberations, the Task Force concluded that --

1. The new Toxicology Protocol has been judged to be sound by a satisfactory process, but continuing review is needed;

2. A nationwide clinical testing program sponsored and supported by NCI has led to many chemotherapeutic agents now widely used in cancer. Approximately 40,000 patients annually survive because of these drugs. Some phases of the clinical trials need closer central management;

3. Recently augmented controls on the distribution of anticancer drugs by NCI to its investigators are sound and should minimize or eliminate the problem of drug leakage;

4. Within the limitations of the state-of-the-art, NCI and FDA procedures for addressing ADRs are acceptable for protecting the cancer patient from unnecessary risks;

5. Therapeutic intent exists in Phase I clinical trials involving new anticancer drugs;

5. Protection of the cancer patient through proper informed consent procedures can be improved by adherence to existing HHS and FDA regulations; the IRB and the physician share a major responsibility for the adequacy of the consent process and, in that role, may be helped by educational material provided to them by the sponsor (NCI), OPRR, and FDA;

7. The proper use of sanctions by both FDA and NIH is appropriate and needed against wrongdoing investigators and institutions;

8. The MOU is a useful document in which FDA and NCI may incorporate further managerial and operational understandings that may facilitate the activities in the development and regulation of anticancer drugs.

The Task Force found that recent NCI and FDA changes are positive and reflect efforts to improve management of the anticancer drug development program. The implementation of these changes and the recommendations of the Task Force will help to correct existing problems as the agencies continue to carry out effectively their respective roles. The Task Force believes that cancer patients have been aided and will in the future benefit from the anticancer drug development program.

APPENDIX A

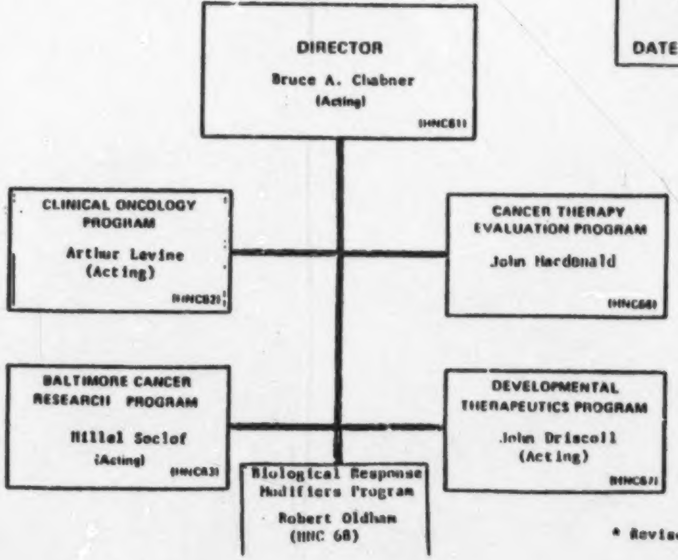
ORGANIZATIONAL CHARTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
National Institutes of Health

National Cancer Institute
Division of Cancer Treatment

APPROVED: DS Fredrickson
DATE: 4/15/81.


DIRECTOR
Bruce A. Chabner
(Acting)
(HNC81)
CLINICAL ONCOLOGY PROGRAM
Arthur Levine
(Acting)
(HNC82)
CANCER THERAPY EVALUATION PROGRAM
John Macdonald
(HNC84)
BALTIMORE CANCER RESEARCH PROGRAM
Hillel Soclof
(Acting)
(HNC83)
Biological Response Modifiers Program
Robert Oldham
(HNC 68)
DEVELOPMENTAL THERAPEUTICS PROGRAM
John Driscoll
(Acting)
(HNC87)
*

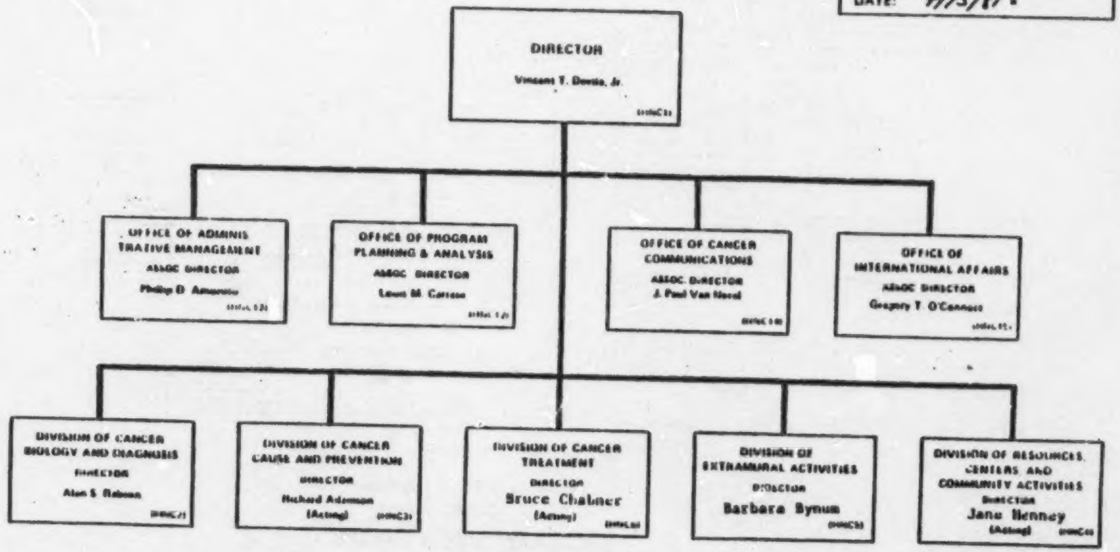
* Revised date 10/2/81

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
National Institutes of Health

APPROVED: Donald S. Fredrickson
DATE: 4/15/81

National Cancer Institute

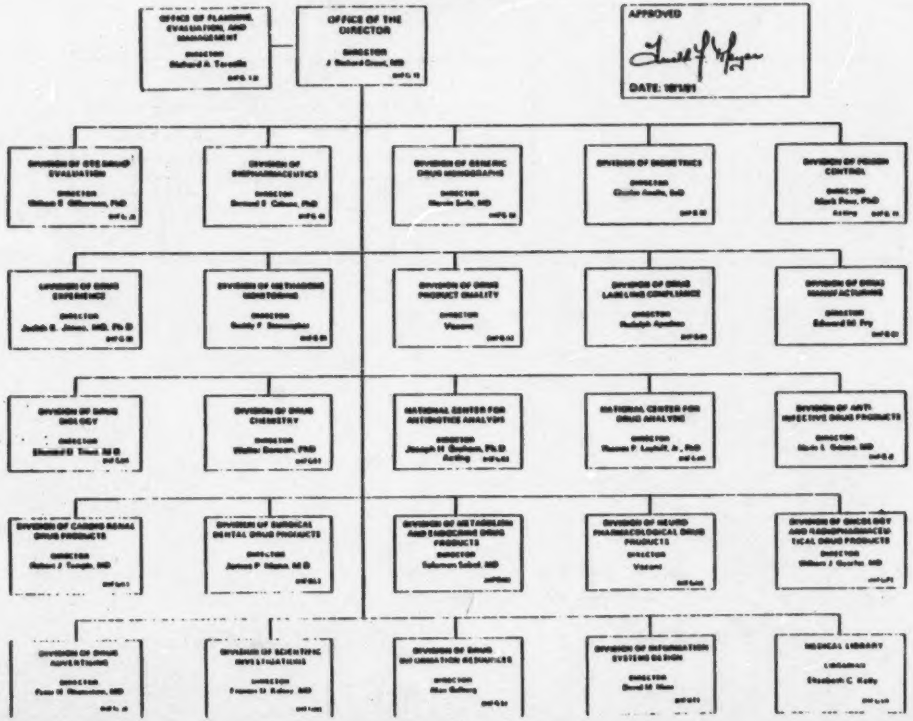

DIRECTOR
Vincent T. DeVita, Jr.
OFFICE OF ADMINISTRATIVE MANAGEMENT
ASSOC DIRECTOR
Philip D. Amoruso
OFFICE OF PROGRAM PLANNING & ANALYSIS
ASSOC DIRECTOR
Louis M. Carrese
OFFICE OF CANCER COMMUNICATIONS
ASSOC. DIRECTOR
J. Paul Van Nevel
OFFICE OF INTERNATIONAL AFFAIRS
ASSOC DIRECTOR
Gregory T. O'Conor
DIVISION OF CANCER BIOLOGY AND DIAGNOSIS
DIRECTOR
Alan S. Rabson
DIVISION OF CANCER CAUSE AND PREVENTION
DIRECTOR
Richard Adamson
(Acting)
DIVISION OF CANCER TREATMENT
DIRECTOR
Bruce Chabner
(Acting)
DIVISION OF EXTRAMURAL ACTIVITIES
DIRECTOR
Barbara Bynum
DIVISION OF RESOURCES, CENTERS AND COMMUNITY ACTIVITIES
DIRECTOR
Jane Henney
(Acting)

* Revised June [illegible] '81

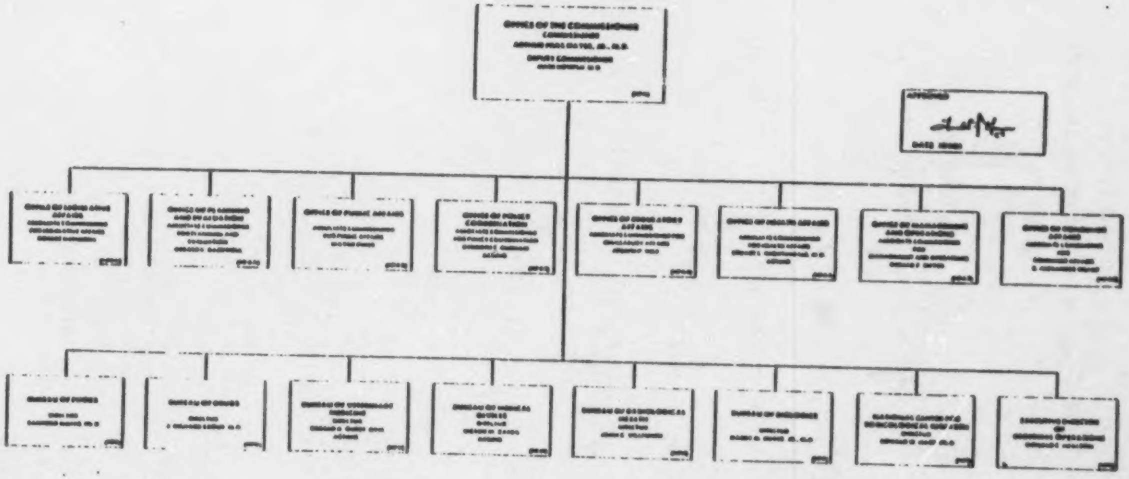
DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
Food and Drug Administration

BUREAU OF DRUGS


OFFICE OF PLANNING, EVALUATION, AND MANAGEMENT
DIRECTOR
OFFICE OF THE DIRECTOR
DIRECTOR
J. Richard Crout, MD
APPROVED
DATE: 10/1/81
DIVISION OF OTC DRUG EVALUATION
DIRECTOR
William E. Gilbertson
DIVISION OF BIOPHARMACEUTICS
DIRECTOR
Bernard E. Cabana, PhD
DIVISION OF GENERIC DRUG MONOGRAPHS
DIRECTOR
Marvin Seife, MD
DIVISION OF BIOMETRICS
DIRECTOR
Charles Anello, ScD
DIVISION OF POISON CONTROL
DIRECTOR
Acting
DIVISION OF DRUG EXPERIENCE
DIRECTOR
Judith K. Jones, MD, Ph.D
DIVISION OF METHADONE MONITORING
DIRECTOR
DIVISION OF DRUG PRODUCT QUALITY
DIRECTOR
Vacant
DIVISION OF DRUG LABELING COMPLIANCE
DIRECTOR
Rudolph Apodaca
DIVISION OF DRUG MANUFACTURING
DIRECTOR
Edward M. Fry
DIVISION OF DRUG BIOLOGY
DIRECTOR
DIVISION OF DRUG CHEMISTRY
DIRECTOR
Walter Benson, PhD
NATIONAL CENTER FOR ANTIBIOTICS ANALYSIS
DIRECTOR
Acting
NATIONAL CENTER FOR DRUG ANALYSIS
DIRECTOR
Thomas P. Layloff, Jr., PhD
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
DIRECTOR
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
DIRECTOR
Robert J. Temple, MD
DIVISION OF SURGICAL-DENTAL DRUG PRODUCTS
DIRECTOR
DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS
DIRECTOR
Solomon Sobel, MD
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
DIRECTOR
Vacant
DIVISION OF ONCOLOGY AND RADIOPHARMACEUTICAL DRUG PRODUCTS
DIRECTOR
William J. Gyarfas, MD
DIVISION OF DRUG ADVERTISING
DIRECTOR
Peter H. Rheinstein, MD
DIVISION OF SCIENTIFIC INVESTIGATIONS
DIRECTOR
Frances O. Kelsey, MD
DIVISION OF DRUG INFORMATION RESOURCES
DIRECTOR
DIVISION OF INFORMATION SYSTEMS DESIGN
DIRECTOR
MEDICAL LIBRARY
LIBRARIAN
Elizabeth C. Kelly

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION



APPENDIX B

PERSONNEL INTERVIEWED BY THE TASK FORCE

NATIONAL CANCER INSTITUTE PERSONNEL INTERVIEWED BY THE NATIONAL CANCER INSTITUTE - FOOD AND DRUG ADMINISTRATION TASK FORCE ON INVESTIGATION NEW DRUGS

Chabner, Dr. Bruce A.
  Acting Director, Division of Cancer Treatment

DeVita, Dr. Vincent T., Jr.
  Director, National Cancer Institute

DeWys, Dr. William
  Acting Chief, Clinical Investigations Branch
  Division of Cancer Treatment

Driscoll, Dr. John
  Acting Director for Developmental Therapeutics
  Developmental Therapeutics Program
  Division of Cancer Treatment

Henney, Dr. Jane
  Special Assistant for Clinical Affairs
  Division of Cancer Treatment

Hoth, Dr. Daniel B.
  Chief, Investigational Drug Branch
  Cancer Therapy Evaluation Program
  Division of Cancer Treatment

Kisner, Dr. Daniel L.
  Deputy Associate Director, Cancer Therapy Evaluation Program
  Division of Cancer Treatment

Lowe, Dr. Michael C.
  Acting Chief, Toxicology Branch
  Developmental Therapeutics Program
  Division of Cancer Treatment

Macdonald, Dr. John S.
  Associate Director, Cancer Therapy Evaluation Program
  Division of Cancer Treatment

Mackie, Ms. Elise
  Program Analyst, Cancer Therapy Evaluation Program
  Division of Cancer Treatment

Marsoni, Dr. Silvia
  Chief, Drug Evaluation and Reporting Section
  Investigational Drug Branch
  Cancer Therapy Evaluation Program
  Division of Cancer Treatment

NCI Personnel Interviewed

Schepartz, Dr. Saul A.
Deputy Director, Division of Cancer Treatment

Vilk, Mr. Paul J.
Pharmacist, Cancer Therapy Evaluation Program
Division Of Cancer Treatment

FOOD AND DRUG ADMINISTRATION PERSONNEL
INTERVIEWED BY THE NATIONAL CANCER INSTITUTE - FOOD AND DRUG ADMINISTRATION TASK FORCE ON INVESTIGATIONAL NEW DRUGS

Brisson, Mr. Ernest L.
  Director, Bioresearch Monitoring Staff
  Office of Regulatory Affairs

Crout, Dr. J. Richard
  Director, Bureau of Drugs

Finkel, Dr. Marion J.
  Associate Director for New Drug Evalution
  Bureau of Drugs

Guarino, Dr. Anthony M.
  Pharmocologist, Division of Oncology and Radiopharmaceutical Drug Products
  Bureau of Drugs

Gyarfas, Dr. William J.
  Director, Division of Oncology and Radiopharmaceutical Drug Products
  Bureau of Drugs

Hamric, Ms. Kay
  Staff Assistant to the Commissioner, Food and Drugs

Hayes, Dr. Arthur Hull, Jr.
  Commissioner, Food and Drugs

Hensley, Dr. Michael J.
  Medical Officer, Clinical Investigations Branch
  Division of Scientific Investigations
  Bureau of Drugs

Johnson, Dr. John R.
  Medical Officer, Oncology Section, Division of Oncology and
  Radiopharmaceutical Drug Products
  Bureau of Drugs

Kelsey, Dr. Frances O.
  Director, Division of Scientific Investigations
  Bureau of Drugs

Lisook, Dr. Alan B.
  Chief, Clinical Investigations Branch
  Division of Scientific Investigations
  Bureau of Drugs

Nightingale, Dr. Stuart
  Acting Associate Commissioner for Health Affairs

Ottes, Mr. Ronald T.
  Deputy Executive Director of Regional Operations

FDA Personnel

Richman, Dr. David J.
Supervisory Pharmacologist, Division of Oncology and Radiopharmaceutical Drug Products
Bureau of Drugs

Ripper, Ms. Leah W.
Consumer Safety Officer, Division of Oncology and Radiopharmaceutical Drug Products
Bureau of Drugs

Turner, Dr. Gurston D.
Pharmacologist, Division of Scientific Investigations
Bureau of Drugs

Walker, Dr. Howard L.
Supervisory Medical Officer, Oncology Section
Division of Oncology and Radiopharmaceutical Drug Products
Bureau of Drugs

Wilms, Mr. Heinz G.
Deputy Director, Division of Scientific Investigations
Bureau of Drugs

Wood, Ms. Rebecca
Supervisor of Chemistry Reviews
Division of Oncology and Radiopharmaceutical Drug Products
Bureau of Drugs

Young, Dr. Robert S.K.
Medical Officer, Oncology Section
Division of Oncology and Radiopharmaceutical Drug Products
Bureau of Drugs

OTHER PERSONS
INTERVIEWED BY THE NATIONAL CANCER INSTITUTE - FOOD AND DRUG ADMINISTRATION TASK FOR ON INVESTIGATIONAL NEW DRUGS

Bernard, Ms. Sharon
  Human Resources Division
  U.S. General Accounting Office

Brandt, Dr. Edward N., Jr.
  Assistant Secretary for Health
  Department of Health and Human Services
  Public Health Service

Capron, Mr. Alexander Morgan
  Executive Director, President's Commission for the Study of Ethical Problems in Medicince and Biomedical and Behavioral Research

Fenstermaker, Mr. Carl
  Group Director
  Human Resources Division
  U.S. General Accounting Office

Horton, Ms. Linda
  Deputy Chief Counsel for Regulations and Hearings
  Office of the General Counsel
  Deparment of Health and Human Services
  Public Health Service

McCarthy, Dr. Charles R.
  Director, Office for Protection from Research Risks
  Office of the Director
  National Institutes of Health

MacKay, Dr. Charles R.
  Deputy Director, Office for Protection from Research Risks
  Office of the Director
  National Institutes of Health

Michie, Mr. James F.
  Chief Investigator, Subcommittee on Investigations and General Oversight of the Committee on Labor and Human Resources, United States Senate

Mishkin, Ms. Barbara
  Deputy Director, President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research

Parker, Ms. Terri Kay
  Subcommittee on Investigations and General Oversight of the Committee on Labor and Human Resources, United States Senate

Other Persons Interviewed

Raub, Dr. William F.
Associate Director for Extramural Research and Training
Office of the Director
National Institutes of Health

Reyds, Dr. Robert B.
Vice President, G. H. Besselaar Associates
Princeton, New Jersey
Contractor to NCI to Clinical Trials Monitoring Service

Smith, Dr. Craig G.
Director, Systems Consulting
Mathtech, A Division of Mathematics, Inc.
Princeton, New Jersey
Contractor to NCI to Clinical Trials Monitoring Service

APPENDIX C

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
October 5, 1981	Meeting of Task Force Members Only		
October 9, 1981	Dr. J. Richard Crout, Director, Bureau of Drugs, FDA	X	
	Dr. Marion J. Finkel, Associate Director for New Drug Evaluation, Bureau of Drugs, FDA	X	
	Dr. Bruce A. Chabner, Acting Director, Division of Cancer Treatment, NIH	X	
	Dr. Jane Henney, Acting Deputy Director, National Cancer Institute, NIH	X	
October 14, 1981	Meeting of Task Force Members Only		
October 19, 1981	Meeting of Task Force Members Only		
October 20, 1981	Dr. Jane Henney		X
October 22, 1981	Dr. John S. Driscoll, Acting Associate Director for Developmental Therapeutics, Division of Cancer Treatment, NCI, NIH (also Head, Drug Design Chemistry Section, Laboratory of Medicinal Chemistry and Biology, Developmental Therapeutics Program, DCT, NCI, NIH)	X	
	Dr. Michael C. Lowe, Acting Chief, Toxicology Branch, Developmental Therapeutics Program, DCT, NCI, NIH	X	

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
October 22, 1981 (Continued)	Dr. John S. Macdonald, Associate Director, Cancer Therapy Evaluation Program, DCT, NCI, NIH	X	
	Dr. Daniel B. Hoth, Chief, Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment, NCI, NIH	X	
October 26, 1981	Dr. Daniel B. Hoth	X	
	Dr. John S. Macdonald	X	
	Ms. Kay Hamric, Staff Assistant to the Commissioner, FDA		X
October 27, 1981	Mr. William Dommel, Assistant Director, Office for Protection from Research Risks, OD, NIH		X
	Dr. Charles R. McCarthy, Director, Office for Protection from Research Risks, OD, NIH		X
	Dr. Charles R. McKay, Deputy Director, Office for Protection from Research Risks, OD, NIH		X
October 28, 1981	Dr. Charles R. McCarthy		X
	Dr. Charles R. McKay		X
October 29, 1981	Dr. Daniel B. Hoth		X
	Dr. Robert S.K. Young, Medical Officer, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, FDA	X	

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
November 4, 1981	Dr. William J. Gyarfas, Director, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, FDA	X	
	Dr. Michael J. Hensley, Medical Officer, Division of Scientific Investigations, Bureau of Drugs, FDA	X	
November 5, 1981	Dr. Craig G. Smith, Director, Systems Consulting, Mathtech, A Division of Mathematica, Inc., Contractor to NCI to Clinical Trials Monitoring Service	X	
	Dr. Robert B. Royds, Vice President, G.H. Besselaar Associates, Contractor to NCI to Clinical Trials Monitoring Service	X	
	Dr. Daniel B. Hoth	X	
	Dr. Anthony M. Guarino, Pharmacologist, Division of Oncology and Pharmaceutical Drug Products, Bureau of Drugs, FDA	X	
	Mr. Ernest L. Brisson, Director, Bioresearch Monitoring Staff, Office of Regulatory Affairs, FDA	X	
November 9, 1981	Mr. Heinz G. Wilms, Deputy Director, Division of Scientific Investigations, Bureau of Drugs, FDA	X	

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
November 9, 1981 (Continued)	Dr. Frances O. Kelsey, Director, Division of Scientific Investigations, Bureau of Drugs, FDA	X	
	Dr. Marion J. Finkel, Associate Director for New Drug Evaluation, Bureau of Drugs, FDA	X	
	Dr. Charles R. McCarthy	X	
November 12, 1981	Mr. Alexander Morgan Capron, Executive Director and	X	
	Ms. Barbara Mishkin, Deputy Director President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research	X	
	Dr. Howard L. Walker, Supervisory Medical Officer, Oncology Section, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, FDA	X	
	Ms. Laurie Meade, Field Inspector, FDA	X	
	Mr. Ronald T. Ottes, Deputy Executive Director, Regional Operations, FDA	X	
	Dr. Michael J. Hensley	X	
November 13, 1981	Dr. Jane Henney		X
November 16, 1981	Dr. Daniel B. Hoth		X

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
November 19, 1981	Ms. Leah W. Ripper, Consumer Safety Officer Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, FDA	X	
	Dr. John R. Johnson, Medical Officer, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, FDA	X	
	Dr. Rebecca H. Wood, Supervisor of Chemistry Reviews, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs	X	
	Dr. Stuart L. Nightingale, Acting Associate Commissioner for Health Affairs, FDA	X	
November 20, 1981	Mr. Carl Fenstermaker, Group Director, Human Resources Division, U.S. General Accounting Office (GAO)		X
	Ms. Sharon Bernard, Human Resources Division, U.S. GAO		X
November 23, 1981	Dr. Edward N. Brandt, Jr., Assistant Secretary for Health	X	
	Dr. William F. Raub, Associate Director for Extramural Research and Training, NIH	X	
	Dr. Alan B. Lisook, Chief, Clinical Investigations Branch, Division of Scientific Investigations, Bureau of Drugs, FDA	X	

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
November 24, 1981	Dr. Frances O. Kelsey		X
	Mr. Heinz G. Wilms		X
	Dr. John S. Macdonald		X
	Dr. Saul A. Schepartz, Deputy Director Division of Cancer Treatment, NCI, NIH		X
	Dr. Richard Simon, Chief, Biometric Research Branch, Division of Cancer Treatment, NCI, NIH		X
November 25, 1981	Meeting of Task Force Members Only		
November 30, 1981	Meeting of Task Force Members Only		
December 1, 1981	Dr. John S. Macdonald	X	
	Dr. Daniel B. Hoth	X	
	Dr. Gurston D. Turner, Division of Scientific Investigations, Bureau of Drugs, FDA	X	
	Dr. Daniel L. Kisner, Deputy Associate Director, Cancer Therapy Evaluation Program, DCT, NCI, NIH	X	
	Dr. William DeWys, Acting Chief, Clinical Investigations Branch, DCT, NCI, NIH	X	

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
December 3, 1981	Mr. James F. Michie, Chief Investigator and	X	
	Ms. Terri Kay Parker, Staff Counsel, Subcommittee on Investigations and General Oversight, Committee on Labor and Human Resources, U.S. Senate	X	
December 11, 1981	Dr. J. Richard Crout	X	
December 14, 1981	Meeting of Task Force Members Only		
December 16, 1981	Dr. Vincent T. DeVita, Jr., Director, NCI	X	
December 17, 1981	Dr. Arthur Hull Hayes, Jr., Commissioner, Food and Drugs	X	
December 21, 1981	Meeting of Task Force Members Only		
December 23, 1981	Meeting of Task Force Members Only		
January 4, 1982	Meeting of Task Force Members Only		
January 7, 1982	Meeting of Task Force Members Only		

APPENDIX D

LIST OF ADDITIONAL MEETINGS OF THE TASK FORCE

(Also see Appendix C)

CHRONOLOGICAL LIST OF TASK FORCE MEETINGS

	DATE	PRESENTORS	FULL TASK FORCE MEETING	SMALL GROUP MEETING
	January 18, 1982	Task Force Members Only		
	January 21, 1982	Task Force Members Only		
	January 22, 1981	Task Force Members Only		

APPENDIX E

SOME SOURCE MATERIALS AVAILABLE TO THE TASK FORCE

The following list provides a representation of materials distributed to the Task Force or made available in the Task Force staff offices. This list does not generally include (1) much descriptive information developed by FDA and NCI staff for the Task Force in response to inquiries of the Task Force members, e.g., flow charts, raw data, and analyses from FDA and NCI, (2) agenda or minutes, and (3) internal working memoranda and draft reports.

Material is arranged generally in the order in which it was provided to the Task Force.

A more comprehensive list of materials available to the Task Force has been prepared.

TASK FORCE ON
NATIONAL CANCER INSTITUTE - FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUGS

Turner/Meade Inspection Report on NIH/NCI/Division of Cancer Treatment, dated September 21, 1981.

Memorandum of Understanding - NIH/FDA.

NCI Drug Master File.

Memorandum dated August 19, 1980, to Commissioner, Food and Drug Administration, from R. S. K. Young, M.D., Ph.D., subject: "21 CFR 10.75 request for internal agency review of Dr. Crout's decision to 'accept' the NCI's master file."

Memorandum dated May 29, 1981, to Commissioner, Food and Drug Administration, from R. S. K. Young, M.D., Ph.D., subject: "Follow up: 21 CFR 10.75 internal agency review of NCI drug master file."

Memorandum dated December 13, 1979, to Director, Bureau of Drugs (HFD-1), from Marion J. Finkel, M.D., Associate Director for New Drug Evaluation (HFD-100), subject: "NCI-Division of Cancer Treatment (DCT) Drug Master File (DMF) 2903 - ACTION MEMORANDUM."

Memorandum dated December 12, 1979, to Marion J. Finkel, M.D., Associate Director for NDE (HFD-150), from William J. Gyarfas, M.D, Director, DORDP (HFD-150), subject: "NCI Division of Cancer Treatment's (DCT) Drug Master File (DMF) 2903."

Memorandum dated June 3, 1981, to Director, Bureau of Drugs, HFD-1, from Stuart L. Nightingale, M.D., Acting Associate Commissioner for Health Affairs, HFY-1, subject: "Dr. Robert S. K. Young's Petition Regarding the NCI's Testing Toxicology Guidelines."

Title 21 - Food and Drugs, Section 10.30, "Citizen petition;" Section 10.33, "Administrative reconsideration of action."

Letter dated December 27, 1979, to Dr. Vincent DeVita, M.D., Director, DCT, NCI, from J. Richard Crout, M.D., Director, Bureau of Drugs, subject: "Your Drug Master File submitted in accordance with the Memorandum of Understanding between the NCI and FDA published in the May 1, 1979, Federal Register."

Memorandum dated June 26, 1981, to Acting Director, DCT, NCI, and Associate Director, CTEP, DCT, NCI, from Daniel F. Hoth, M.D., Chief, IDB, CTEP, DCT, NCI, subject: "Meeting with Mr. Jim Michie, Staff Investigator of the Subcommittee on Investigations and Oversight, Senate Committee on Labor and Human Resources."

Letter dated July 9, 1981, to Senator Paula Hawkins from Vincent F. DeVita, Jr., M.D., Director, NCI, subject: "Information relating to the July 13 National Cancer Institute site visit to the M.D. Anderson Hospital is supplied as requested in your letter of July 8."

Letter dated July 8, 1981, to Dr. Vincent T. DeVita, Jr., Director, National Cancer Institute, from Senator Paula Hawkins, subject: "Request certain information concerning the National Cancer Institute's scheduled site visit to the M.D. Anderson Cancer Center in Houston, Texas, on July 13, 1981."

Note to Dr. Brandt from Florence Hassell, undated, subject: "NCI IND Review," with attachment "Tentative Agenda for Meeting with Senator Paula Hawkins (R-Fla.), Friday, September 18, 1981, (rescheduled for September 23), 10 A.M."

Note, undated, to Dr. Brandt from Florence Hassell, subject: "Review of the National Cancer Institute (NCI) Investigational New Drug Problem."

Letter dated July 9, 1981, to Secretary Schweiker from Senator Paula Hawkins, subject: "Telephone conversation concerning my request for temporary assignment of a physician-scientist from the Department...to the Subcommittee staff...."

Letter dated July 31, 1981, to Secretary Schweiker from Senator Paula Hawkins, subject: "Your generous offer of temporarily assigning to the Subcommittee staff Dr. Michael Hensley...."

Letter dated August 24, 1981, to Senator Paula Hawkins from Secretary Schweiker, subject: "...your letter of July 9 concerning your request to have Dr. Michael Hensley detailed to the staff...."

Memorandum dated September 10, 1981, to Florence Hassell, Program Analyst, Planning and Evaluation, OASH, from Jane E. Henney, M.D., subject: "Requested Material: National Cancer Institute's Drug Development Program."

Memorandum dated August 28, 1981, to Director, NCI, from Bruce A. Chabner, M.D., Acting Director, DCT, NCI, subject: "Supporting Data to Reply to the Letter from Senator Hawkins."

Memorandum dated August 20, 1981, to Acting Director, Division of Cancer Treatment, NCI, from John S. Macdonald, M.D., Associate Director, Cancer Therapy Evaluation Program, subject: "Supporting Data to Reply to the Points Brought up in the Letter from Hawkins."

Chlorozotocin and Renal Failure

"Point 1": A discussion of renal failure following treatment with Chlorozotocin.

"Chronology of Chlorozotocin Renal Toxicity."

References List

Baker, J.; Lokey, J. L.; et al. New England Journal of Medicine Vol. 301 12 (1979): 662.

Letter dated January 15, 1981, to Dr. C. J. Cornell, Dartmouth Medical School from Dickerman Hollister, M.D., The New York Hospital-Cornell Medical Center, subject: "What may be an instance of chlorozotocin induced renal failure."

Adverse Reaction Report Form dated January 14, 1981; investigator, Dickerman Hollister, M.D.; name of drug, Chlorozotocin; reaction, renal failure.

Memorandum dated February 23, 1981, to All Principal Investigators from Luz Hammershaimb, M.D., Special Assistant to the Chief, IDB, subject: "Adverse Drug Reaction to Chlorozotocin (NSC 178248)."

"A Clinical Trial of Chlorozotocin (NSC-178248), DTIC, and Actinomycin D in Metastatic Malignant Melanoma."

Methyl-CCNU and Leukemia

"Point #2": A discussion of acute leukemia in three patients which may have been caused by MeCCNU.

"Chronology of Events since January 1, 1981."

"Reported Cases by Individual Investigators of AML, Pre-Leukemias and Smouldering Leukemias" (Flow Chart).

Letter dated January 16, 1981, to Jack Killen, M.D, Project Officer, GITSG, Clinical Investigations Branch, CTEP, DCT, NCI, from E. Douglas Holyoke, M.D., Chief, Department of Surgical Oncology, subject: "Letter from Dr. Mayer of Sidney Farber Institute and a report of leukemia patient from Georgetown, dated January 19, 1980, with letter attached to E. Douglas Holyoke from Robert J. Mayer."

Memorandum to GITSG Colorectal PIs from John Y. Killen, Jr., M.D., subject: "Acute Leukemia in Patients on GI 6175."

Letter dated March 25, 1981, to FDA, Bureau of Drugs, HFD-150, from National Cancer Institute (Sponsor), per: John S. Penta, Ph.D., Head Drug Regulatory Affairs Section, Investigational Drug Branch, subject: "...followup to...telephone call on March 24, 1981...concerning possible adverse drug effects following the administration of the drug Methyl CCNU."

Memorandum For the Record dated March 30, 1981, from Acting Chief, Investigational Drug Branch, CTEP, DCT, NCI, subject: "Methyl CCNU Leukemia Cases."

Letter dated April 6, 1981, to all investigators using MeCCNU, from Daniel F. Hoth, M.D., Chief Investigational Drugs Branch, CTEP, DCT, NCI, subject: "Possible adverse drug effects following the administration of MeCCNU."

Mitoxantrone and Cardiotoxicity

"Point #3": A discussion of adverse effects to patients after having been administered Mitoxantrone (DHAD).

"Chronology of Reports of Cardiotoxicity Related to Mitoxantrone Therapy."

Flow Chart of "Mitoxantrone Cariotoxicity."

Prestudy form concerning patient given Mitoxantrone at St. Jude Children's Research Hospital; New Agent Study Sheet concerning same patient; and Off Study Summary of same patient.

Memorandum dated April 6, 1981, to Louise Lev, M.D., Drug Monitor, IDB, from Richard Ungerleider, M.D., Special Assistant for Pediatrics, subject: "Possible Cardiac Toxicity From Mitoxantrone."

Letter dated June 17, 1981, to FDA, Bureau of Drugs, HFD-150, from National Cancer Institute (Sponsor), per: John S. Penta, Ph.D., Head, Drug Regulatory Affairs Section, Investigational Drug Branch, subject: "Report four patients who developed congestive heart failure which may be related to administration of the drug Mitoxantrone..."

Letter dated June 17, 1981, to "Dear Investigator," from Louise M. Lev, M.D., Special Assistant to the Chief, IDB, CTEP, DCT, subject: "Possible adverse drug effects following the administration of Mitoxantrone (DHAD)."

Memorandum dated June 22, 1981, to Chief, IDB, from Special Assistant to the Chief, IDB, subject: "ADR-Mitoxantrone."

Memorandum dated July 13, 1981, to Chief, IDB, from Special Assistant to the Chief, IDB, sujbect: "Mitoxantrone Cardiotoxicity."

Letter dated July 14, 1981, to All Mitoxantrone Investigators, author unknown, subject: "Mitoxantrone Cardiotoxicity."

Letter to FDA, Bureau of Drugs, HFD-150, from John S. Penta, Ph.D., Head, Drug Regulatory Affairs Section, IDB, CTEP, DCT, NCI, subject: "...followup to the telephone report given to Dr. Johnson of your administration on July 7, 1981, concerning two suspected adverse drug reactions due to the drug Mitoxantrone (NSC 301739), (IND 16802)."

Letter dated July 30, 1981, to Dr. Daniel Hoth, IDB, NCI, from Ronald L. Stephens, M.D., Associate Professor of Medicine, Director, Division of Clinical Oncology, The University of Kansas, subject: "...case of...DHAD related cardiotoxicity."

Letter dated August 5, 1981, to FDA, Bureau of Drugs, HFD-150, from National Cancer Institute (Sponsor), per: Daniel F. Hoth, M.D., Chief, Investigational Drug Branch, CTEP, subject: "...letter from Dr. Ronald Stephens, the University of Kansas, reporting a case of cardiotoxicity in a middle-aged man being treated with Mitoxantrone."

Letter dated June 23, 1981, to Louise Lev, M.D., IDB, DCT, NCI, from Charles B. Pratt, M.D., St. Jude Children's Research Hospital, re: Patient treated with adriamycin and dihydroxy anthracenedione.

Letter dated July 15, 1981, to Louise Lev, M.D., IDB, DCT, NCI, from Charles B. Pratt, M.D., re: His letter of June 23, 1981, with regard to patient who developed cardiomyopathy following treatment with dihydroxy anthracenedione.

Flow Chart of Phase II Study of dihydroxy anthracenedione.

Letter dated July 9, 1981, to Louise Lev, M.D., IDB, DCT, NCI, from Charles B. Pratt, M.D., re: His letter of June 23, 1981, with regard to patient who developed cardiomyopathy after being given dihydroxy anthracenedione, with a copy of summary of treatment of patient attached.

Letter dated July 14, 1981, to Dr. John Durant, SECSG Statistical Officer, University of Alabama in Birmingham, from Gerald L. Logue, M.D., Chief, Hematology-Medical Oncology, Veterans Administration, re: Patient Joseph Faircloth who was noted to have cardiovascular difficulty after receiving Mitoxantrone, and a copy of patient's history attached.

Letter dated July 15, 1981, to Louise Lev, M.D., from Phillip A. Desimone, M.D., Chief, Hematology Section, enclosing a copy of the outline of the history of Mr. William Harp, the man with questionable toxicity to Mitoxantrone.

Letter dated August 12, 1981, to FDA, Bureau of Drugs, HFD-150, from NCI (Sponsor), per: Daniel F. Hoth, M.D., Chief, IDB, CTEP, subject: "Report on cardiotoxicity in a patient being treated with Mitoxantrone.

M.D. Anderson Issue

"Chronological Sequence of Events Concerning Human Pharmacological Studies of 5-MeTHHF."

"Point #4": A discussion concerning NCI report to FDA of use of radiolabeled drug in four patients without NCI-approved IND.

Memorandum dated August 6, 1981, to Acting Director, NIH, from Director, NCI, subject: "Recommendations Regarding Ti Li Loo, Ph.D., and the M.D. Anderson Hospital and Tumor Institute, University of Texas System Cancer Center."

Memorandum dated August 6, 1981, to Acting Director, NIH, from Director, NCI, subject: "Presentation of the Site Visit to M.D. Anderson."

Memorandum dated July 24, 1981, to Director, NCI, through: Acting Director, DCT, NCI, from Deputy Director, DCT, NCI, subject: "Clinical Pharmacology Study of 5-Methyltetrahydrohomofolate (NSC-139490) Carried Out at M.D. Anderson Hospital and Tumor Institute (University of Texas System Cancer Center): Summary Report of NIH Site-Visit Team."

Memorandum dated August 5, 1981, to Director, NCI, through: Acting Director, DCT, NCI, from Deputy Director, DCT, NCI, re: Followup on M.D. Anderson Site Visit.

Memorandum dated August 5, 1981, to Deputy Director, Division of Cancer Treatment, NCI, from Chief, Investigational Drug Branch, CTEP, DCT, NCI, subject: "Return Site Visit to M.D. Anderson Hospital on July 28, 1981."

Background Information on M.D. Anderson Site Visit, July 13, 1981.

IND and Liver Failure

"Point #5": A discussion concerning patients who died of liver failure after receiving the drug Indicine-N-Oxide (I-N-O).

"Chronology of Indicine-N-Oxide Hepatotoxicity."

Indicine-N-Oxide Severe Hepatoxicity Table.

Annual Report to the Food and Drug Administration, Indicine-N-Oxide, IND 13952, NSC 132319, April 1980, Drug Sponsor: Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute.

Memorandum for the Record dated September 30, 1981, from Irene Schifren, subject: "Meeting with Senator Hawkins' Staff on September 29, 1981, Room 508-B."

Memorandum dated October 1, 1981, from Irene Schifren, subject: "NCI/FDA Hearings."

Undated note to Dr. Brandt, through Jim Friedman, from Florence Hassell, subject: "NCI IND Review" with attachment "Tentative Agenda for Meeting with Senator Paula Hawkins (R. Fla.), Friday, September 18, 1981, 10 a.m."

Letter dated July 29, 1981, to Orrin G. Hatch from Vincent T. DeVita, Jr., M.D., transmitting April 28, 1981, memorandum from Henry A. Kirshenmann, Jr., to DHHS, subject: "Proposed Plan to Correct Deficiencies Noted in the IG's Follow-up Report on NCI Contracting." (Interim Report) Addendum to Interim Report: Letter dated September 14, 1981, to Paula Hawkins from Vincent T. DeVita, Jr., M.D.

Statement by Vincent T. DeVita, Jr., M.D., Director, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205, before the Senate Committee on Labor and Human Resources, June 2, 1981.

"NCI Contracting Practices." Hearing Report Summary (Subcommittee on Investigations and General Oversight of the Committee on Labor and Human Resources, U.S. Senate), National Institutes of Health, Division of Legislative Analysis, June 2, 1981.

"Oversight of the National Cancer Program" Hearing before the Subcommittee on Investigations and General Oversight of the Committee on Labor and Human Resources, United States Senate, Ninety-seventh Congress, First Session, on the National Cancer Program: A Progress Report, May 21, 1981.

"NCI Oversight." Hearing Report Summary (Subcommittee on Investigations and General Oversight of the Committee on Labor and Human Resources, U.S. Senate) National Institutes of Health, Division of Legislative Analysis, May 21, 1981.

"Falsification of Research Data and Institutional Pressures of Research." Hearing Report Summary (Investigations and Oversight Subcommittee of House Committee on Science and Technology), National Institutes of Health, Division of Legislative Analysis, March 31 and April 1, 1981.

Letter dated January 19, 1979, to Donald S. Fredrickson from Donald Kennedy transmitting "Memorandum of Understanding Relative to Anti-Cancer Drug Development."

Organizational Charts

National Cancer Institute
National Cancer Institute, Division of Cancer Treatment
Food and Drug Administration
Food and Drug Administration, Bureau of Drugs

"NCI Preclinical Toxicology Protocol," Dr. Michael C. Lowe's (Acting Chief, Toxicology Branch, Division of Cancer Treatment, NCI) summary before National Cancer Advisory Board, October 5, 1981.

Letter dated December 13, 1978, to Dr. Vincent T. DeVita, Jr., from Dr. J. Richard Crout transmitting Marcel Rosenzweig's, et al., "Animal Toxicology for Early Clinical Trials of Anti-cancer Agents," Cancer Clinical Trials April 21-28, 1981.

"National Cancer Institute Protocol for Changing Preclinical Toxicology Protocol for Antineoplastic Agents," a paper provided in the Spring 1979 to DCT Board of Scientific Counselors for October 1979 meeting.

Excerpt from Minutes of October 29-30, 1979, Meeting of DCT Board of Scientific Counselors.

Drug Master File 2903, Book 4, "New Toxicolgy Protocol," March 7, 1980.

Letter dated March 9, 1981, to Dr. Marion F. Finkel from Saul A. Schepartz, re: Evaluation of oncolytic agents.

Minutes of July 9, 1979, Meeting of the Toxicology Guidelines Subcommittee of the Oncologic Drugs Advisory Committee, Bureau of Drugs, FDA.

Minutes of October 11-12, 1979, Meeting of Oncologic Drugs Advisory Committee.

Amended Protocol for Single Dose Range Finding and Lethality Study in Mice, April 23, 1981.

Minutes of June 11-12, 1981, Meeting of the Board of Scientific Counselors, DCT, NCI.

Letter dated October 1, 1981, to Dr. J. Richard Crout from Bruce A. Chabner, re: FDA staff' questions about NCI preclinical trial Toxicology Protocol.

Prieur, David J., et al. "Procedures for Preclinical Toxicologic Evaluation of Cancer Chemotherapeutic Agents: Protocols of the Laboratory of Toxicology." Cancer Chemotherapy Reports Part 3, Vol. 4, No. 1 (January 1973).

Goldsmith, M. S., et al. "Quantitative Prediction of Drug Toxicity in Humans from Toxicology in Small and Large Animals." Cancer Research Vol. 35 (May 1975): 1354-1364.

Guarino, Anthony M., et al. "Adequacies and Inadequacies in Assessing Murine Toxicity Data with Antineoplastic Agents." Cancer Research Vol. 39 (June 1979): 2204-2210.

Overview of Congressional Interest in Adverse Drug Reactions in the NCI Drug Development Program.

"Treatment Linear Array," Division of Cancer Treatment, NCI, December 1976.

DCT Bulletin, September 1980.

"The Drug Development and Clinical Trials Programs of the Division of Cancer Treatment," NCI, Cancer Clinical Trials.

Letter dated May 22, 1981, to Mrs. Eppie Lederer, of Field Newspaper Syndicate, from Dr. Vincent DeVita, Jr., with attachments.

Memorandum, undated, to Director, Bureau of Drugs, through Deputy Director, FDA, from Associate Director for New Drug Evaluation, subject: "Toxicology Guidelines for Cytotoxic Anticancer Agents - Dr. Young's Petition of March 5, 1980, to the Commissioner."

"Clinical Investigations, Proposed Establishment of Regulations on Obligations of Sponsors and Monitors," DHHS/FDA, Federal Register (Tuesday, September 27, 1977).

"Obligations of Clinical Investigators of Regulated Articles, Proposed Establishment of Regulations," DHHS/FDA, Federal Register Part V (Tuesday, August 8, 1978).

Letter dated October 9, 1981, to Dr. Bruce Chabner from Marion J. Finkel, re: Requested revisions to updated Drug Master File and attached Flow Chart of Adverse Drug Reaction.

"Clinical Testing for Safe and Effective Drugs." USDHHS/PHS/FDA, No. (FDA) 74-3015, January 1981.

"A Primer on New Drug Development." USDHHS/PHS/FDA/Office of Public Affairs, No. (FDA) 74-3021, Reprinted from February 1974, Re-issued November 1979.

"Institutional Review Boards; Request for Information." DHHS/FDA, Federal Register Vol. 46, No. 176 (Friday, September 11, 1981), Notices (45539-45539.)

Letter dated October 16, 1981, to Senate Subcommittee on Labor and Human Services and Education, Committee on Appropriations; Senate Committee on Labor and Human Resources, House Subcommittee on Labor and Human Services and Education, House Subcommittee on Health and Environment, from Dr. Vincent T. DeVita, Jr., re: Washington Post articles on cancer.

Letter dated October 12, 1981, to Mr. Jonathan Newman (sic) from Brigid G. Leventhal, re: Drug DHAD.

Washington Post Series on Cancer Chemotherapy, Office of Cancer Communication, NCI.

Gup, Ted, and Neumann, Jonathan. "Experimental Drugs: Death in the Search for Cures." The War on Cancer, First Do No Harm, Part 1, The Washington Post, 18 October 1981, p. A1 and following.

Gup, Ted, and Neumann, Jonathan. "Risk, Rivalry and Research - and Error." The War on Cancer, First Do No Harm, Part 2, The Washington Post, 18 October 1981, p. A1 and following.

Memorandum dated March 5, 1980, to Commissioner of FDA, from Robert S. K. Young, M.D., subject: "Petition for internal agency review of the Bureau Director's (J. Richard Crout, M.D.) decision to implement a token toxicology testing program for anticancer drugs." (Citizen Petition)

Drafts of NCI letters to Clinical Investigators on new procedures for reporting adverse drug reactions - responsibilities of investigators.-

Memorandum dated August 20, 1981, to Special Assistant for Clinical Affairs, DCT, NCI, through: Associate Director, CTEP, DCT, NCI, and Acting Associate Director, DTP, DCT, NCI, from J. Paul Davignon (Chief, PRB, DTP, DCT, NCI) and Daniel F. Hoth (Chief, IDB, CTEP, DCT, NCI), subject: "Response to Drug Distribution Policies Memorandum, Dated July 12, 1981."

Flow Chart of Adverse Drug Reaction (ADR) from NCI Drug Master File.

"National Cancer Institute, Clinical Trials (In Thousands of Dollars)," October 20, 1981.

Gup, Ted, and Neumann, Jonathan. "The World of Shattered Hopes." The War on Cancer, Anatomy of a Clinic, Part 3, The Washington Post, 20 October 1981, p. A1 and following.

Gup, Ted, and Neumann, Jonathan. "Spark of Hope Vs. Ordeal of Pain: Dilemma of Drug Researchers." The War on Cancer, Anatomy of a Clinic, Part 4, The Washington Post, 21 October 1981, p. A1 and following.

"Hill Hearings on Cancer Drugs Planned." The Washington Post, 20 October 1981, p. A24.

Memorandum dated September 16, 1981, to Acting Director, Division of Cancer Treatment, NCI, from Chief, Investigational Drug Branch, CTEP, subject: "Proposal for Monitoring of Clinical Trials via Periodic Site Visits."

"Division of Cancer Treatment Pre-clinical Decision Making Process" and attachments.

"Protocol Toxicology Studies" and attachments.

Appendix 6, Standard Operating Procedures for Quality Assurance in the Battelle Columbus Laboratories Toxicology Program Office.

Form FD 1573, "Statement of Investigator."

"The War on Cancer." Congressional Record, S. 11610 - S. 11619, U. S. Senate, October 19, 1981.

"The Operational Plan and Procedures for Clinical Trials." The Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, January 24, 1973.

"Monitor's Report." September 30, 1981, Investigational Drug Branch, National Cancer Institute.

"Clinical Studies." September 30, 1981, Investigational Drug Branch, National Cancer Institute.

Hearing Report, "Drug Regulation Report--Orphan Drugs." Highlights, First Session, 97th Congress No. 2 (April 24, 1981) Division of Legislative Analysis, NIH.

"Status of INDs Filed by NCI 1971-81," October 1981, provided by Dr. Jane Henney, NCI.

"Cancer - A Progress Report." Newsweek Magazine, November 2, 1981, pp. 94-100.

"Letters to the Editor." *The Washington Post*, 25 October 1981.

"Policies and Procedures for New Drug Testing in Division of Cancer Treatment (DCT), National Cancer Institute: *Outline for President's Cancer Panel*" with attachments, handouts from the President's Panel on Cancer Meeting of October 27, 1981.

"*Survival Statistics: Then and Now*," handout from the President's Panel on Cancer Meeting of October 27, 1981.

Memorandum dated October 23, 1981, to Director, NCI, from Charles R. McCarthy, Ph.D., Director, OPRR, OD, subject: "Recently Published Allegations of Misuse of Cancer Research Drugs."

Statements by Stuart L. Nightingale, M.D., Acting Associate Commissioner for Health Affairs, FDA, before the Subcommittee on Investigations and Oversight, Committee on Science and Technology, House of Representatives, April 1, 1981.

Memorandum dated October 26, 1981, to Clinical Investigations from Bruce A. Chabner, M.D., Director, Division of Cancer Treatment, subject: "Importance of immediate reporting of adverse reactions among patients treated with investigational drugs supplied under an NCI held IND."

45 CFR 46, Revised as of January 26, 1981, and Certain Other Related Laws and Regulations on Protection of Human Subjects.

"Sample Assurance for an Institution Which Currently Has No Multiple Project (General) Assurance on File with HHS and Which Has Submittted a Project to HHS for Funding and Been Requested to File a Single Project (Special) Assurance...." August 5, 1981.

"Cancer Drug Programs Rapped at Hill Hearing." *The Washington Post*, 23 October 1981, p. A3.

Letter dated October 24, 1981, to the Editor, *The Washington Post*, from Charles L. Vogel, M.D., Clinical Director, Comprehensive Cancer Center for the State of Florida, concerning the *Washington Post* story entitled "The World of Shattered Hopes."

Statement of Alexander Morgan Capron, Executive Director (accompanied by Barbara Mishkin, Deputy Director) of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, before the Waxman/Gore Hearings, October 27, 1981.

Statement of John E. Ultmann, M.D., Professor, Department of Medicine, Section of Hematology/Oncology, The University of Chicago, before the Waxman/Gore Hearings, October 27, 1981.

Statement of Emil J. Freireich, M.D., and Ruth Harriet Ainsworth, Professor, The University of Texas System Cancer System, M.D. Anderson Hospital and Tumor Institute before the Waxman/Gore Hearings, October 27, 1981.

Statement of Dr. Solomon Garb (for inclusion in the Hearing Record), physician and Clinical Professor of Medicine at the University of Colorado Medical School, submitted October 25, 1981, for the Waxman/Gore Hearings, October 27, 1981.

Description of Procedures Regulating Clinical Trials within Cooperative Group - Drs. Paul Carbone, Edwin M. Jacobs, and Franco M. Muggia, June 9, 1976.

Kurtz, Howie. "U. S. Cancer Institute Institute Faulted." The Washington Post, 4 November 1981, pp. A1 and A10.

Memorandum dated March 2, 1981, to Director, FDA, Bioresearch Monitoring Staff, FDA, from Deputy Director, Division of Scientific Investigations, subject: "FY 80 Annual Report--Human Drugs Bioresearch Monitoring."

Letter dated January 30, 1980, to Donald F. Tapley from Robert C. Wetherall, Jr., re: a compliance problem.

Memorandum dated July 21, 1980, to Joseph P. Hile, Associate Commissioner for Regulatory Affairs, FDA, from Deputy Director, Bureau of Drugs, FDA, subject: "Interviews of Research Subjects Policy."

Memorandum dated July 21, 1980, to Frances O. Kelsey, Ph.D., M.D., Director, Division of Scientific Investigations, from Jerome A. Halperin, Deputy Director, Bureau of Drugs, subject: "Policy of Human Subject Interviews."

"Interviews of Research Subjects." Compliance Policy Guide, July 7, 1980, (Draft).

Memorandum dated January 11, 1980, to Director, Bureau of Drugs, FDA, through, Deputy Associate Director for New Drug Evaluation, FDA, from Heinz Wilms, Deputy Director, Division of Scientific Investigations, FDA, subject: "Clinical Investigator Stratified Surveillance Strategy."

Memorandum dated December 25, 1979, to Deputy Director, Division of Scientific Investigations, from Director, Bureau of Drugs, FDA, through Deputy Associate Director for New Drug Evaluation, subject: "Clinical Investigator Stratified Surveillance Strategy--ACTION MEMORANDUM," with copy of Stratified Surveillance Strategy for Selecting Clinical Investigator Assignments Under Compliance Program #7348.881 attached.

Staff Manual Guide, Food and Drug Administration, Organization and Delegation Manual. Bureau of Drugs, Division of Scientific Investigations, FDA 1236.9 (January 10, 1980).

Staff Manual Guide, Food and Drug Administration. Bureau of Drugs, Division of Scientific Investigations, "Operating Policies," BD 4810.0 (September 12, 1980).

Staff Manual Guide, Food and Drug Administration. Bureau of Drugs, Division of Scientific Investigations, "New Drug Evaluation," BD 4831.1 (August 14, 1980).

Staff Manual Guide, Food and Drug Administration. Bureau of Drugs, Division of Scientific Investigations, "IND Medical Review Guidelines," BD 4831.1 (August 14, 1980).

Staff Manual Guide, Food and Drug Administration. Bureau of Drugs, Division of Scientific Investigations, "NDA Medical Guideline, Attachment B" (August 14, 1980).

Memorandum dated February 5, 1980, to NDE Reviewing Division's Director, FDA, through Deputy Associate Director for New Drug Evaluations (Scientific) from Associate Director for New Drug Evaluations, subject: "Medical Review Guidelines."

Memorandum dated in 1979 to Dr. Vera C. Glocklin, Supervisory Pharmacologist, FDA, from Director, Division of Scientific Investigations, FDA, subject: "Good Laboratory Practice Regulations--Implementation of Statements Required in Final Reports."

Memorandum dated July 18, 1980, to Division Directors HFD-110-130 FDA, from Associate Director for New Drug Evaluation, FDA, subject: "Non-M.D.s as Clinical Investigators and Monitors."

Statement by Robert S. K. Young, M.D., Ph.D., FDA, before the Subcommittee on Health and the Environment and Subcommittee on Investigations and Oversight, U.S. House of Representatives, October 27, 1981.

Report of Hearings on Orphan Drugs - H.S. 1663 - before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, House of Representatives, March 9, 1981.

Second Inspection of NIH, NCI, IRB, Assigned by the Bureau of Drugs for the First Quarter of FY 81, Inspection date: November 20, 1980.

"Responsibility in Advertising: An Oncologist's View." Letter to the Editor of The New England Journal of Medicine: Vol. 301, No. 18, (November 1, 1979) : 1004.

"Who Reviews the Ads?", editorial, The New England Journal of Medicine Vol. 301, No. 18: p. 999.

Letter to the Editor, signed by Dr. Robert S. K. Young, M.D., Ph.D., The New England Journal of Medicine (January 31, 1980). (provided by Dr. Young)

Muggia, Franco M., M.D. (with a Commentary by Emil J. Freireich, M.D.) "Anticancer Drug Development and Federal Regulation: Protection Against Progress?" The American Journal of Medicine Vol. 71, (September 1981): 341-344.

Testimony of Fitzhugh Mullan, M.D. (physician and cancer patient) before the Subcommittee on Health and the Environment, Committee on Energy and Commerce and Subcommittee on Oversight and Investigations, Committee on Science and Technology, October 27, 1981.

Testimony of Gail J. Povar, M.D., Clinical Internist, Teacher of Medical Ethics, George Washington University, before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, and Subcommittee on Oversight and Investigations, Committee on Science and Technology, October 27, 1981.

Statements of James F. Holland, M.D., Professor and Chairman of the Department of Neoplastic Disease, Mount Sinai School of Medicine of New York, before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, and Subcommittee on Oversight and Investigations, Committee on Science and Technology, October 27, 1981.

"Allegedly Withheld Drug Data, U.S. Cancer Institute Faulted." The Washington Post, 4 November 1981, pp. A1 and A10.

"Description of Procedures Regulating Clinical Trials Within the Cooperative Groups." Prepared by Drs. Paul P. Carbone, Edwin M. Jacobs, and Franco M. Muggia, June 9, 1976. (provided by Dr. Hoth)

"A Phase I Study of Diammine (1,1) cyclobutane dicarbixylato (2-1-0,01) platinum (CBDCA; NSC 241240) Administered on a Weekly Schedule, Principal Investigator: Paul V. Woolley, M.D., Co-Investigator: Eric M. Bonnem, M.D., Division of Medical Oncology, Georgetown University Hospital and Vincent T. Lombardi Cancer Research Center, To Be Conducted Under NCI Contract No. 1-97208 Investigational Drug Branch."

Meisel, J. D., and Roth, Loren, H., M.D., M.P.H. "What We Do and Do Not Know About Informed Consent: An Overview of the Empirical Studies." Presented at 1980 Annual Meeting of the American Psychiatric Association, San Franciso, May 8, 1980.

"Clinical Trials Monitoring Service, Monitor's Report." August 31, 1981.

Materials furnished by Mr. Ernest L. Brisson at his presentation to Task Force on November 5, 1981:

"Bioresearch Monitoring Program Administration"
"Bioresearch Monitoring Program Elements"
"BMP Inspection Accomplishment FY 80"
"BMP Regulations"
"Educational Activities"
"Significant Policies"
"Interagency BMP Activities"
"International BMP Activities"
"Accomplishment Data and Evaluation" (Tables 10 and 11)

"Evolution of the National Cancer Institute Master Plan for Drug Development and Interactions with the Food and Drug Administraation." May 15, 1981, unidentified NCI staff (noted especially in November 5, 1981, Hearings of Senate Subcommittee on Investigations and General Oversight).

Human Drugs--Bioresearch Monitoring Briefing for the Commissioner and Staff (FDA) August 27, 1981--Pre-Briefing material.

Mr. Capron's and Ms. Mishkin's statement before Senate Subcommittee on Investigations and General Oversight, November 5, 1981.

"Chapter 5: Possible Recommendations," from the Biennial Report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.

Memorandum dated November 5, 1981, to Ms. Kay Hamric, Staff Assistant to the Commissioner, FDA, from Dr. J. Richard Crout, forwarding a copy of Dr. Finkel's memorandum in response to Task Force questions.

Memorandum dated August 6, 1981, to Acting Director, NIH, from Director, NCI, subject: "Recommendations Regarding Ti Li Loo, Ph.D., and the M.D. Anderson Hospital and Tumor Institute, University of Texas System Cancer Center," with attachments.

Freedom of Information Request dated October 20, 1981, from Dr. Bradford Gray.

"Annotations." NCI Site Visit Report by B. Mishkin.

Letter dated April 5, 1978, to R. Lee Clark, M.D., from John Jennings, M.D., Associate Commissioner for Medical Affairs, re: FDA's inspection of M.D. Anderson Surveillance Committee.

Draft "OPRR Testimony To Be Delivered before Senator Hawkins, Friday, November 6, 1981."

MeCCNU Background provided by Mr. Wilms on November 10, 1981..

FDA Inspection of Montague Lane, M.D., Baylor College of Medicine, November 25 and December 5, 1980.

Memorandum dated November 6, 1981, to Lowell T. Harmison from Ernest L. Brisson, Director, Bioresearch Monitoring Staff, FDA, subject: "IRB Compliance Program/Regulatory Options."

Some briefing materials for Dr. Brandt for testimony at hearings on November 7, 1981.

Statement by Dr. Robert S. K. Young before the Senate Subcommittee on Investigations and General Oversight on November 3, 1981.

Statement by Dr. David J. Richman before the Senate Subcommittee on Investigations and General Oversight on November 3, 1981.

UPI news release after November 6, 1981, Senate hearings.

"Warning Pledge on Cancer Effects." The Washington Post, 7 November 1981, p. A11.

"Improvements in Ten IRB Problem Areas." Bureau of Drugs, FDA, November 1980.

Cassileth, Barrie R., Ph.D.; Zupkins, Robert V., Ph.D.; Sutton-Smith, Katherine, M.S.; and March, Vicki, B.D. "Informed Consent--Why Are Its Goals Imperfectly Realized?" The New England Journal of Medicine (April 17, 1980).

Muss, Hyman B., M.D.; White, Douglas R., M.D.; Michielutte, Robert, Ph.D.; Richards, Frederick, II, M.D.; Cooper, M. Robert, M.D.; Williams, Sarah, B.S.; Stuart, John J., M.D.; and Spurr, Charles L., M.D. "Written Informed Consent in Patients With Breast Cancer." American Cancer Society.

Harmon, William E., M.D.; Cohen, Harvey J., M.D., Ph.D.; Schneeberger, Eveline E. M.D.; and Grupe, Warren E., M.D. "Chronic Renal Failure in Children Treated with Methyl CCNU." The New England Journal of Medicine (May 24, 1979).

Carter, Stephen K., M.D. "Cancer Treatment and Cancer Control: The Dynamic Interaction Between Clinical Research and Community Oncology." The Pharos (Fall 1981).

"Pharmacology and Toxicology in Oncolytics Submitted by Drug Industry" (Details in Oncology INDAs of Industry). (provided by Dr. Guarino on November 5, 1981)

Letter dated April 13, 1978, to Assistant Associate Director for New Drug Evaluation (Chemistry), NCI's INDs, from Charles S. Kumkumian, Ph.D.

Letter dated April 13, 1978, to Dr. J. Richard Crout, Director, Bureau of Drugs, from Vincent T. DeVita, Jr., M.D., Director, Division of Cancer Treatment, NCI.

Letter dated March 24, 1978, to Director, DCT, NCI, through, Associate Director, DTP, DCT, NCI, from J. Paul Davignon, Chief, Pharmaceutical Resources Branch, DTP, DCT, NCI.

Letter dated March 10, 1978, to Investigational Drug Branch, National Cancer Institute, Attention: J. S. Penta, Ph.D., National Institutes of Health, from William J. Gyarfas, M.D., Director, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs.

Letter dated March 13, 1978, to Investigational Drug Branch, National Cancer Institute, from William J. Gyarfas, M.D., Director, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs.

"IND 7581/semustine/methyl CCNU, IND 4595/lomustine-CeNU, and IND 969/carmustine-BiCNU." Draft written (revised April 2, 1981) by Bureau Staff; edited by Dr. Crout; sent to Dr. Vincent T. DeVita, Jr., Director, NCI; and mentioned in Senate hearing of November 6, 1981.

"Title 21--Food and Drugs, Chapter I--Food and Drug Administration, Department of Health and Human Services (Docket No. 77N-0195) Obligations of Sponsors and Monitors of Clinical Investigations." (draft provided by Mr. Wilms on November 10, 1981)

Letter dated March 6, 1978, to Dr. Donald Kennedy, Commissioner of Food and Drugs, Food and Drug Administration, from Robert C. Hickey, M.D., Executive Vice President and Director, The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston, Texas, and R. Lee Clark, M.D., President, The University of Texas System Cancer Center.

Letter dated April 5, 1978, to R. Lee Clark, M.D., President, The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, Texas Medical Center, from John Jennings, M.D., Associate Commissioner for Medical Affairs, re: IRB inspection.

Letter dated June 22, 1978, to Dr. R. Lee Clark, M.D., President, The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, from Roland B. Shepherd, Supervisory Investigator.

DeVita, Dr Vincent T. Jr. "A Pioneering Chemotherapist Is the Bureaucracy's Point Man in the Drive To Lick Cancer--And the Target of Impatient Critics." People Weekly, November 16, 1981.

"President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research." A brochure.

"Protecting Human Subjects, First Biennial Report to the President and the Congress on the Adequacy and Uniformity of the Rules and Policies, and their Implementation, for the Protection of Human Subjects of Biomedical and Behavioral Research, 1981." Partial preliminary draft, October 9, 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavorial Research.

Memorandum dated April 22, 1981, to Donald S. Fredrickson, M.D., Director, NIH, from Richard J. Riseberg, Office of the General Counsel, Public Health Division, subject: "Options available to BIDs in considering whether to make or continue grant awards to scientists who have engaged in improper activity."

"Department of Health and Human Services, Office of the Secretary, 45 CFR 76." Federal Register Vol. 45, No. 198, Rules and Regulations (October 9, 1980): 67252-67269.

"Report to the Subcommittee on Science, Research, and Technology, House Committee on Science and Technology--FDA Drug Approval--A Lengthy Process that Delays the Availability of Important New Drugs." The Comptroller General of the United States, United States General Accounting Office, May 28, 1980.

Letter dated August 27, 1981, to The Honorable Richard S. Schweiker, The Secretary for Health and Human Services, from Gregory J. Ahart, Director, Human Resources Division, U.S. General Accounting Office, enclosing a copy of draft report to Congressman James H. Scheuer which discusses FDA's efforts to speed up the drug review process.

Statement on the Food and Drug Administration's Efforts to Speed Up the Drug Review Process (for release on delivery September 16, 1981) by Edward A. Densmore, Deputy Director, Human Resources Division, U.S. General Accounting Office, before the Subcommittee on Natural Resources, Agriculture Research, and Environment, House Committee on Science and Technology.

Memorandum dated April 2, 1981, to the Secretary from Acting Commissioner of Food and Drugs, subject: "N[illegible] Investigation: Methyl CCNU - Gore Subcommittee Hearing, 4-1-81."

"FDA Compliance Programs in Bioresearch Monitoring," signed by Dr. Charles R. MacKay, Deputy Director, OPRR, NIH, May 19, 1980, and Helen M. Crown, Chief, Grants and Assistance Ageements Section, FDA, May 23(?), 1980, with attachments: "Clinical Investigator Status Summary, 3/1/81," and "Interagency Agreement Between the National Institutes of Health and the Food and Drug Administration."

Draft Memorandum of Understanding (MOU) between FDA and NIH, Office of Protection From Research Risks (OPRR).

"Notification of Third Parties of Disqualification Procedures: Issues" with attachments: a note dated December 19, 1980, to Linda Horton from Ernest L. Brisson enclosing memorandum dated July 31, 1980, to Bioresearch Monitoring Program Managers, from Robert A. Dobratz, subject: "Proposed Policy Third Party Notification."

"Civil and Criminal Sanctions: Disqualification and Prosecution," with attachments.

Memorandum dated March 27, 1981, to the Acting Commissioner, from John C. Petricciani, M.D., Director, Bioresearch Monitoring Program, subject: "Termination of Assignment," with attachments.

Memorandum dated April 22, 1981, to The Commissioner, from Stuart L. Nightingale, M.D., Acting Associate Commissioner for Health Affairs, subject: "Meeting with Dr. Frederickson (sic) to Discuss Methods to Improve Communications Between NIH and FDA," with attachments.

"NIH Liaisons for Bioresearch Monitoring Program," with attachment.

"Memo of Meeting," dated March 31, 1981, and signed by Stuart L. Nightingale, M.D. subject: "Meeting to Discuss Congressman Gore's Hearing on Fraud in Science.

Memorandum dated November 18, 1981, to Ronald T. Ottes, from Joan P. Porter, subject: "Questions from Task Force on NCI/FDA INDs."

Letter dated November 12, 1981, with enclosure, to Dr. Harmison from Robert B. Royds, Vice President of G. H. Besselaar Associates.

Memorandum dated November 20, 1981, to Dr. Marion J. Finkel, Dr. Frances O. Kelsey, and Mr. Heinz G. Wilms, from Chairman, Task Force on NCI/FDA INDs, subject: "Requests of FDA for Information."

Notes of Ms. Leah Ripper given to the Task Force on November 19, 1981, concerning her investigation of five INDs: Indicine-N-Oxide; Pyrazolo-imidazole (IMPY); Necarzinostatin (NCS) (Zinostatin); Streptozotcn (Streptoxocin) (SZT) (Zanosar); Mercaptrourine-5 (6-MP) (Purinethol).

Sponsor-Monitor Regulations - (Latest Internal Draft, November 12, 1981) provided by Mr. Wilms.

"Hawkins Persists in Attacks on NCI Despite Testimony Refuting Charges." The Cancer Letter Vol. 7, No. 46 (November 13, 1981) : 7-9.

"Cancer Institute's Drug Program Reproved." Science Vol. 214 (November 20, 1981): 887-889.

Memorandum dated February 2, 1976, to Associate Director for New Drug Evaluation, from Dr. Crout, Director, Bureau of Drugs, subject: "Clinical Holds on Oncology INDs."

Background material from Dr. Nightingale's presentation to Task Force on November 19, 1981.

"Hearings Find Differences at FDA Between Executives, Midlevel Staff." The Cancer Letter Vol. 7, No. 47 (November 20, 1981): pp. 4-7.

Letter dated November 25, 1981, to Joan P. Porter from Ronald T. Ottes, Deputy Executive Director of Regional Operations, HFO-2. Attachments to the letter include - Copy of assignments to Baltimore District that led to inspection of Methyl CCNU at NCI in 1979; copy of the Agostino consumer complaint of adverse reaction to Methyl CCNU; and additional background information.

Barth Hoogstraten, M.D., American Cancer Society Professor of Clinical Oncology, Professor of Medicine, Department of Internal Medicine, University of Kansas Medical Center, ed. Cancer Research--Impact of the Cooperative Groups. Masson Publishing USA, Inc., 1980.

Cancer Therapy Abstracts Vol. 20, No. 10 (February 1980), The Franklin Press: Philadelphia, Pennsylvania.

List of GAO Reports issued involving FDA, May 22, 1967, through October 23, 1981.

"Federal Control of New Drug Testing Is Not Adequately Protecting Human Test Subjects and the Public." GAO Report, July 15, 1976.

Excerpt from memorandum dated November 10, 1981, to Dr. Charles McCarthy from Stuart L. Nightingale, M.D., commenting on the President's Commission Draft Biennial Report of October 9, 1981.

Memorandum dated November 20, 1981, to Joan P. Porter, Executive Secretary, Task Force, from Dr. Saul A. Schepartz, Deputy Director, Division of Cancer Treatment, NCI, transmitting copy of briefing book on the Methyl CCNU nephrotoxicity problem, and a portion of the books on other drugs.

Memorandum dated November 20, 1981, to the Chief, Clinical Investigations Branch, Division of Scientific Investigations, from Michael J. Hensley, M.D., subject: "Contact with Jim Michie."

Memorandum dated November 18, 1981, to Telecon between Dr. John Sproull, Health and Welfare, Ottawa, Canada, and Frances O. Kelsey, Ph.D., M.D., Director, Division of Scientific Investigations, Bureau of Drugs.

"Review Panel on New Drug Regulation, May 1977." Final Report, Department of Health, Education, and Welfare.

Title 21--Food and Drugs, Part 312--New Drugs for Investigational Use, Subparts A, B, and C.

"General Considerations for the Clinical Evaluation of Drugs." U.S. Department of Health, Education, and Welfare, September 1977.

Note dated November 12, 1981, to Dr. Brandt, from Dick Kusserow, Office of Inspector General, DHHS, with attached letter to Senator Paula Hawkins dated November 13, 1981, also from Dick Kusserow.

Minutes of the Phase I-II Working Group Meeting, June 2-3, 1981, Investigational Drug Branch, Cancer Therapy Evaluation Program, National Cancer Institute.

Copy of M.D. Anderson IRB Inspection by Bureau of Biologics in March 1981 and in August/September 1979.

Memorandum dated November 25, 1981, to Dr. Harmison, from John R. Johnson, M.D., Oncology Group, FDA, subject: "Clinical Monitoring of Studies with New Investigational Cancer Drugs."

"Task Force on Drug Approval." FDA Talk Paper, September 3, 1981.

Charge to the Federal Drug Approval Process (McMahon Commission) from the House Committee on Science and Technology. (provided by Dr. Nightingale on December 2, 1981)

Memorandum dated November 25, 1981, to Deputy Director, DCT, NCI, from Computer Systems Analyst, CTEP, DCT, NCI, subject: "Review of Computer Resource Contracts." (provided by Dr. Kisner, NCI, December 1, 1981)

Memorandum dated April 30, 1980, to Acting Director, DCT, NCI, from Special Assistant to the Chief, IDB, subject: "Methyl CCNU Nephrotoxicity.

Memorandum dated December 3, 1981, to Acting Deputy Director, NCI, from Executive Secretary, IND Task Force, subject: "Follow-up Questions Regarding Toxicology Protocol."

Memorandum dated January 6, 1981, from Associate Director for Extramural Research and Training, NIH, subject: "Institutions, Organizations and Principal Investigators Under Investigation by the Division of Management Survey and Review, NIH, or Other Government Units (1752)."

Memorandum dated November 20, 1981, to Dr. Marion J. Finkel, Associate Director for New Drug Evaluation, FDA, from Chairman, NCI/FDA Task Force, subject: "Requests of FDA for Information."

Memorandum dated October 29, 1981, to Director, Bureau of Drugs (HFD-1), from Associate Director for New Drug Evaluation (HFD-100), subject: "Data Audit of Clinical Investigators of Anti-Cancer Drugs - ACTION."

Letter to John Penta, Ph.D., Division of Cancer Treatment, from William J. Gyarfas, M.D., Director, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, re: Claimed Investigational Exemption for New Drug for Thymosin Fraction 5 (IND 18,264) and Synthetic Thymosin Alpha (IND 19,255).

Letter dated September 16, 1981, to Vincent H. Bono, M.D., National Cancer Institute, from Joyce Creamer, Consumer Safety Officer, subject: "Claimed Investigational Exemption (IND) for 2-DCF (2-deoxycoformycin)."

Letter dated July 27, 1981, to Mr. Irminger, Adria Laboratories, Inc., from William J. Gyarfas, M.D., Director, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, subject: "Claimed Investigational Exemption for New Drug (IND) for Cisplatin Injectable (NSC 119875)."

Letter dated September 18, 1981, to Richard A. Raffa, Senior Project Coordination Manager, Sandoz, Inc., from William J. Gyarfas, M.D., Director, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, subject: "Claimed Investigational Exemption (IND) for a New Drug 27-400 (cyclosporin A) Intravenous Infusion."

Letter dated September 23, 1981, to Frank N. Nelson, Jr., Roswell Park Memorial Institute, from William J. Gyarfas, M.D., Director, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, subject: "Claimed Investigational Exemption (IND) for VP-16 and DDP in the treatment of advanced testicular cancer."

Letter dated September 23, 1981, to Daniel F. Hoth, M.D., National Cancer Institute, from William J. Gyarfas, M.D, Bureau of Drugs, re: for homoharringtonine (NSC 141633).

Letter to Daniel Hoth, M.D., NCI, from William J. Gyarfas, M.D., Bureau of Drugs, re: for Tricyclic Neuleoside 5' Phosphate (IND 18,905) and homoharringtonine (IND 19,125); with attachment, Medical Officer Review of IND 19,125.

Finished Review, September 10, 1981, Division of Oncology and Radiopharmaceutical Drug Products - IND 19,125.

Finished Review, September 10, 1981, Pharmacology and Toxicology Review of IND 19,125.

Letter to John S. Penta, Ph.D., NCI, from William J. Gyarfas, M.D., Bureau of Drugs, re: Tricyclic Nucleoside 5'Phosphate (NSC 230594).

Medical Officer Initial Review of IND 18,615, April 23, 1981.

Initial Review and Evaluation of Pharmacology and Toxicology Data - IND 18,616 (April 17, 1981).

Division of Oncology and Radiopharmaceutical Drug Products - Chemist's Review #1 - IND 18,615 (April 14, 1981).

Letter to John S. Penta, Ph.D., NCI, from William J. Gyarfas, M.D., Bureau of Drugs, re: 9, 10-Anthracenedicarboxaldehyde bis, Orange Crush, CL 215.942 - IND 18,412 (April 10, 1981).

Division of Oncology and Radiopharmaceutical Drug Products Medical Officer Review #1 - IND 18,412 (February 23, 1981).

Letter dated October 14, 1981, to Daniel F. Hoth, M.D., NCI, from William J. Gyarfas, M.D., Bureau of Drugs, re: Ethanethiol, 2-(3-aminopropyl) amino-dihydrogen Phosphate (ester) (WR-272); NSC 296961 as a radioprotector in conjunction with radiation therapy in patients with cancer.

Letter dated April 2, 1981, to John S. Penta, Ph.D., NCI, from William J. Gyarfas, M.D., Bureau of Drugs, re: IND 18,318.

Medical Officer Review Consultation (Radiotherapeutic Implications) IND 18,318 - DRUG: WR 2721, a radioprotector (July 9, 1981).

Medical Officer Review of IND 18,318 - WR 2721 (January 15, 1981 - August 25, 1981).

Pharmacology and Toxicology Review of IND 18,318, Original Summary (March 17, 1981).

Division of Oncology and Radiopharmaceutical Drug Products - Chemist's Review #1 - IND 18,318 (March 20, 1981).

Letter dated September 16, 1981, to National Cancer Institute, attention: Dr. Saul Schepartz, from Dr. Gyarfas, subject: "Appropriate form for NCI IND submissions."

Copy of *United States vs. Rutherford*, 99 S. Ct. 2470 (1979).

Carter, Stephen K.; Selawry, Oleg; and Slavik, Milan. "Phase I Clinical Trials, U.S.A. U.S.S.R. Monograph, Methods of Development of New Anticancer Drugs." *National Cancer Monograph* 45 (March 1977) DHEW Publication No. (NIH) 76-1037.

Gottlieb, Jeffrey A. "Phase I and Phase II Clinical Trials: A Critical Reappraisal," a section of: "Pharmacological Basis of Cancer Chemotherapy," *A Collection of Papers Presented at the Twenty-Seventh Annual Symposium of Fundamental Cancer Research, 1974*, published for the *University of Texas System Cancer Center*, M.D. Anderson Hospital and Tumor Institute, Houston, Texas.

List of panelists at "Oversight of the National Cancer Institute" hearing of Senate Subcommittee on Investigations and General Oversight, November 3, 1981,

NIH Public Advisory Groups--Authority Structure Functions Members, *U.S. Department of Health and Human Services, Public Health Service*, National Institutes of Health, Committee Management Staff, NIH Publication No.81-11, January 1981.

Testimony of Charles W. Young, M.D., Chief, Developmental Chemotherapy Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, N.Y., before the Investigations and General Oversight Subcommittee of the Senate Committee on Labor and Human Resources, Senator Paula Hawkins (R. Fla.), Chairperson, on November 3, 1981.

Memorandum dated October 15, 1981, to the Associate Director for New Drug Evaluation, from J. Richard Crout, M.D., Director of the Bureau of Drugs, re: NCI proposed changes to the Toxicolgogy Guidelines.

"Opening Statement of Senator Paula Hawkins, November 3, 1981." *News From Paula Hawkins, United States Senator*.

"Opening Statement of Senator Edward M. Kennedy, Committee on Labor and Human Resources Investigations Subcommittee Hearing, Oversight of National Cancer Institute, November 3, 1981, 10:00 a.m." *From the Office of Senator Edward M. Kennedy of Massachusetts*.

Statement of Senator Gordon J. Humphrey (N.H.) on November 3, 1981.

Annual Site Visit Report by Dr. #1, Principal Physician-Investigator, of a Comprehensive Cancer Center, May 13, 1981, signed by the Contractor Monitor (for NCI).

FDA Inspection (July 22,23, and 28, 1981) of IND-18,411 at a Comprehensive Cancer Center.

FDA Inspection Report (date removed) of a Comprehensive Cancer Center.

Memorandum dated June 3, 1981, to Edward M. Evans, Special Agent in Charge, Washington Field Office, OI, OIG, from the Deputy Assistant Inspector General for Investigations, OIG, subject: "Investigational Drug Branch, NCI, NIH, PHS, DHHS, Bethesda, Maryland; Bristol Laboratories, Syracuse, New York - Possible Conflict of Interest; Malfeasance WF-44-0-94 MIR Code 103." (Attachment to the memorandum: a copy of a report from the Office of Investigations, U.S. Department of Health and Human Services, on the investigation conducted on October 24, 1980, at Rockville, Maryland, by S. A. Linda Little and Robert Sheridan.)

MeCCNU Chronology of DSI's activity to June 11, 1981, prepared and submitted to the Task Force by Heinz Wilms via route slip dated December 4, 1981.

Letter dated October 1, 1981, to J. Richard Crout, M.D, Director, Bureau of Drugs, Food and Drug Administration, from Bruce A. Chabner, M.D., Acting Director, Division of Cancer Treatment, NCI, enclosing (1) a list of specific revisions to the current protocol, and (2) a policy statement as a possible covering document protocol.

Memorandum dated December 14, 1981, to Executive Secretary, PHS Task Force on NCI/FDA IND Process, from Saul A. Schepartz, Deputy Director, Division of Cancer Treatment, NCI, enclosing a copy of material from the Task Six Report of the University of Pittsburgh under contract NCI-CM-87173.

Gray, Branford H.; Cooke, Robert A.; and Tannenbaum, Arnold S., "Research Involving Human Subjects, The performance of institutional review boards is assessed in this empirical study." Science Vol. 201 (September 22, 1978): 1094.

Pharmaceutical Resources Branch, General Information and Operational Protocols, October 30, 1981. (provided by Saul A. Schepartz)

Memorandum (draft) dated July 2, 1981, to Associate Director for New Drug Evaluation, from J. Richard Crout, M.D., Director, Bureau of Drugs, subject: "National Cancer Institute (NCI) Toxicology Guidelines (attached)."

Memorandum dated October 9, 1981, to Acting Director, DCT, NCI, from Acting Chief, Toxicology Branch, DTP, DCT, NCI, subject: "Toxicology questions related to the Senate Subcommittee hearings."

Memorandum dated July 7, 1981, to the Commissioner of Food and Drugs, from Robert S. K. Young, M.D., Ph.D., subject: "Petition for Internal Agency Review and Citizen's Petition National Cancer Institute's Token Toxicology Program."

Memorandum from Arthur Hull Hayes, Jr., M.D., Commissioner, Food and Drugs Administration, to Dr. Robert S. K. Young, subject: "Toxicology Testing Guidelines, enclosing copy of Response to Dr. Robert S. K. Young's Petition."

Minutes of July 9, 1979, Meeting of Toxicology Guidelines Subcommittee of the Oncologic Drugs Advisory Committee, FDA.

Minutes of October 11-12, 1979, Meetings of the Oncologic Drugs Advisory Committee, FDA.

Kovack, John S; Ames, Matthew M.; Powls, Garth; Moertel, Charles G.; Hahn, Richard G.; and Creagan, Edward T. "Toxicity and Pharmacokinetics of a Pyrrolizidine Alkaloid, Indicine N-Oxide, in Humans." *Cancer Research* Vol. 39 (November 1979): 4540-4544.

Annual Report to the Food and Drug Administration, Indicine N-Oxide IND 13952, NSC 132319, April 1980.

DCT Clinical Trials Monitoring Program Goals.

Excerpt from proposed regulations, "Obligations of sponsors and monitors of clinical trials." *Federal Register* (September 1977).

Memorandum for the Record dated May 7, 1981, from Head, Drug Regulatory Affairs Section, IDB, CTE, DCT, NCI, subject: "Telephone Report to FDA Regarding Indicine N-Oxide (NSC 132319) IND 13952."

Annual Report to the Food and Drug Administration, Indicine N-Oxide IND 13952, (NSC 132319), June 1981.

Letter dated November 8, 1981, to Congressman Henry A. Waxman from Edward N. Brandt, Jr., M.D., Assistant Secretary for Health.

"Commissioner's Bureau of Drugs Management Meeting, February 12, 1981, Background Statement on Treatment IND's."

Memorandum dated April 30, 1980, from Vincent H. Bono, Jr., M.D., Chief, Investigational Drug Branch, CTEP, subject: "Lack of Compliance with FDA Regulations in the Misuse of NCI Investigational Agents."

Letter dated May 8, 1981, to Dr. J. Richard Crout, re: response to his letter dated April 6, 1981, re: Nephrotoxicity discovered with the drug Methyl CCNU, as well as other points about NCI's sponsorship of drug trials and its reporting to the FDA.

"Peer Review of Contract Proposals at the National Cancer Institute," information for contract proposals reviewers, Contracts Review Branch, Division of Extramural Activities, NCI, June 1981.

"Procedures of Review of Intramural Research," Division of Cancer Treatment, NCI.

Letter to The Washington Post dated October 19, 1981, from Vincent T. DeVita, Jr., M.D., Director, NCI, re: His reactions about the articles written by Ted Gup and Jonathan Neumann.

Letter to The Washington Post dated October 20, 1981, from Bruce A. Chabner, M.D., Acting Director, Division of Cancer Treatment, NCI, re: Subject of articles are misrepresented.

Letter to The Washington Post dated October 21, 1981, from Vincent T. DeVita, Jr., M.D., Director, NCI, re: A few final comments about the series of articles by Ted Gup and Jonathan Neumann.

"Operational Plan and Procedures for Clinical Trials," the Cancer Therapy Evaluation Program, Division of Cancer Treatment, NCI, revised April 1, 1981.

Memorandum dated September 16, 1981, to Acting Director, Division of Cancer Treatment, NCI, from Daniel F. Hoth, M.D., Chief, Investigational Drug Branch, CTEP, subject: "Proposal for Monitoring of Clinical Trials via Periodic Site Visits."

Memorandum dated September 16, 1981, to Acting Director, Division of Cancer Treatment, NCI, from Daniel F. Hoth, M.D., Chief, Investigational Drug Branch, CTEP, subject: "Accountability of Disposition of Investigational Drugs.

Letter dated September 30, 1981, to Special Assistant for Clinical Affairs, DCT, NCI, through: Associate Director, CTEP, DCT, NCI, Acting Associate Director, DTP, DCT, NCI, from Chief, IDB, CTEP, DCT, NCI, Chief, PRB, DTP, DCT, NCI, re: Response to Drug Distribution Policies Memorandum dated July 12, 1981.

Letter dated October 25, 1981, to Dr. Michael Lowe, Toxicology Branch, NCI, from Michael D. Kastello, Ph.D., D.V.M., Program Director, re: Procedure used by Battelle's Toxicology Program Office to evaluate and select qualified subcontractors for the toxicological evaluation of antineoplastic compounds.

Description of Procedures Regulating Clinical Trials Within the Cooperative Groups, June 9, 1976.

Operating Guidelines for the Biochemical Modulations Advisory Group.

"Two-Stage Plans for Patient Accrual in Phase II Cancer Clinical Trials." Cancer Treatment Reports Vol. 63, No. 11-12 (November/December 1979): 1721-1725.

"The Determination of the Number of Patients Required in a Preliminary and a Follow-up Trial of a New Chemotherapeutic Agent." Journal of Chronic Diseases Vol. 13, No. 4 (April 1961): 346-353.

Excerpt from Minutes of June 11-12, 1981, Meeting of the Board of Scientific Counselors, Division of Cancer Treatment, NCI.

Division of Cancer Treatment Program Review to the National Cancer Advisory Board, November 30, 1981.

Memorandum dated December 23, 1981, to Deputy Director, Division of Cancer Treatment, from Dr. Daniel F. Hoth, Chief, Investigational Drug Branch, subject: "Annual Report Submissions in Past Five Years."

Memorandum dated December 19, 1981, to Task Force from Dr. Alan B. Lisook, Chief, Clinical Investigations Branch, Division of Scientific Investigations, HFD-180, subject: "Perceptions of Special Treatment of NCI."

Fujiwara, Ty K. "A Brief Evaluation of Twenty-four Toxicology Laboratories; Their Compliance with the Final GLP Regulations and a Comparison of Compliance Rates with Two Previous Studies." Division of Scientific Investigations, Nonclinical Laboratory Studies Branch, July 15, 1980.

"Bioresearch Monitoring Program 7348.808, Bureau of Drugs - D.S.I. HFD-190, Inspection Updated as of September 30, 1981."

"Excerpts from Agency-wide FY 80 BiMo Annual Report prepared by Mr. Brisson."

Krauthammer, Charles. "The Ethics of Human Experimentation." The New Republic, December 9, 1981, p. 16.

Updated memorandum to Robert S. K. Young, M.D., from the Commissioner of Food and Drugs, subject: "Response to Your Petition for Internal Agency Review of the Bureau of Drugs' Decision to Approve NCI's Toxicology Testing Guidelines and Citizens' Petition to Revoke the Approval of the Toxicology Testing Guidelines."

Letter dated October 1, 1981, to J. Richard Crout, M.D., Director, Bureau of Drugs, from Bruce A. Chabner, M.D., Acting Director, Division of Cancer Treatment, NCI, re: NCI Preclinical Toxicology Protocol.

Memorandum dated December 29, 1981, to David Fraser, M.D., from Henry Falk, M.D., Chief, Special Studies Branch, Chronic Diseases Division, CEH, CDC, subject: "The Draft Statement Reviewing the NCI/FDA Toxicology Protocol for Cytotoxic Chemotherapeutic Agents."

APPENDIX F

MEMORANDUM OF UNDERSTANDING RELATIVE TO ANTICANCER DRUG DEVELOPMENT

MEMORANDUM OF UNDERSTANDING RELATIVE TO ANTICANCER DRUG DEVELOPMENT

The Division of Cancer Treatment, National Cancer Institute, as a result of its mission, has a substantial and continuing effort of anticancer drug development, the regulation of which comes under the purview of the Food and Drug Administration, primarily but not exclusively within the Bureau of Drugs. A substantial amount of the information available to the Division of Cancer Treatment and to the Bureau of Drugs, acquired by each in the pursuit of their missions, is of common interest to these organizations. In the past, both have been keenly aware of this community of interest and have had extensive informal and effective interchanges of views and of information on a wide variety of problems. Such informal interchanges should and will continue and both organizations encourage the members of their staff to provide the utmost assistance and cooperation in all appropriate areas. In addition, in order to aid in the maintenance of a harmonious, direct working relationship between these two sister organizations, both charged with responsibilities relating to public health, it is believed that a formal Memorandum of Understanding is desirable. The following specific agreements between the National Cancer Institute and the Food and Drug Administration are made to achieve these objectives:

Commitment of the National Cancer Institute

1. The National Cancer Institute designates the Director, Division of Cancer Treatment as the primary contact on matters of policy relative to anticancer drug development. Members of his/her staff responsible for specific aspects of the Drug Development Program will carry on day-to-day contact with their counterparts at the Food and Drug Administration as appropriate.

2. As sponsor of investigational drugs for clinical trial, the Division of Cancer Treatment agrees to comply with all applicable laws, regulations, and any other legal requirements pertaining to such sponsorship.

3. The Division of Cancer Treatment will transmit to the Bureau of Drugs pertinent information generated by the activities of the Division of Cancer Treatment. This will include *Cancer Treatment Reports* and copies of the minutes of pertinent meetings, e.g., the New Drug Liaison Meetings and the Phase I Working Group Meetings. These minutes are not to be considered a substitute for the annual progress reports required for each IND.

4. The Division of Cancer Treatment will designate a member of its staff as a liaison to FDA's Oncology Advisory Committee and will send members of its staff to other Food and Drug Administration meetings, as appropriate, in order to aid communication between the two organizations.

5. The Division of Cancer Treatment will maintain with the Bureau of Drugs a Master File, which will include a detailed description of its overall plan of anticancer drug development, its systems of clinical monitoring, its system of drug distribution and data reporting, pertinent information on Division of Cancer Treatment staff, and other background information normally included in individual Notices of Claimed Investigational Exemption for a New Drug (also known as Investigational New Drug Applications).

   When any portion of the Master File is proposed to be revised in a significant manner, the Division of Cancer Treatment will, prior to such revision, provide a draft copy of the proposed alteration for the Bureau of Drug's comment. Less substantive revisions will be provided to the Bureau of Drugs in finalized form and such revisions will be sent with reasonable promptness. The Division of Cancer Treatment agrees to maintain the Master File in a manner which keeps it current to add information as it believes necessary, or as requested by the Bureau of Drugs, to delete items which are no longer pertinent or active, and to submit to the Bureau of Drugs on or about January 1 of each year a list of the documents it considers to be in the Master File and a certification of their currency and accuracy.

Commitment of the Food and Drug Administration

1. The Food and Drug Administration designates the Associate Director for New Drug Evaluation, Bureau of Drugs, as its primary contact for matters of policy regarding anticancer drugs. Members of his/her staff will interact with appropriate Division of Cancer Treatment staff for day-to-day matters.

2. The Bureau of Drugs will designate appropriate members of its staff as liaison to the Decision Network, the Phase I Working Group, and the New Drug Liaison Meetings and other pertinent meetings of the Division of Cancer Treatment, to aid communication between the Bureau of Drugs and Division of Cancer Treatment.

3. In recognition of the position occupied by the Division of Cancer Treatment in antitumor drug development, and in view of the serious nature of the disease, the Bureau of Drugs agrees to cooperate with and assist the Division of Cancer Treatment in the furtherance of its objectives, to the degree permitted by regulation and law.

4. The Bureau of Drugs agrees to accept the Master File submission of the Division of Cancer Treatment as applicable to all anticancer investigational drugs sponsored by the Division of Cancer Treatment. Information in the Master File will thus be incorporated by reference into all Notices of Claimed Investigational Exemptions (INDs) for anticancer drugs sponsored by the Division of Cancer Treatment.

5. The Bureau of Drugs agrees to bring any deficiencies or problems with the Master File to the attention of the Division of Cancer Treatment

as part of its review and approval of that Master File rather than as comments on specific INDs. If, after a reasonable period needed for correction of the Master File, such correction is not forthcoming, the Bureau of Drugs shall inform the Division of Cancer Treatment which of its INDs may be adversely affected and subject to administrative action.

Commitment of Both the National Cancer Institute and the Food and Drug Administration

If the Director, Division of Cancer Treatment, National Cancer Institute and the Associate Director for New Drug Evaluation, Bureau of Drugs, cannot agree on the appropriate contents of the Master File, or the approvability of the Master File or of any application sponsored by the National Cancer Institute, or on any other matters related to the regulation by the Food and Drug Administration of drugs sponsored by the National Cancer Institute, the matter shall be brought to the attention of the Director of the National Cancer Institute and the Director of the Bureau of Drugs. These persons are then responsible for jointly resolving the matter, either directly or by consultation with, or referral to, the Director of the National Institutes of Health and the Commissioner of Food and Drug. Absent such resolution, final resolution of the matter rests with the Commissioner of Food and Drugs.

FOR THE NATIONAL INSTITUTES OF HEALTH	FOR THE FOOD AND DRUG ADMINISTRATION
By: /s/ Donald S. Fredrickson, M.D.	By: /s/ Donald Kennedy, Ph.D.
Title: Director, NIH	Title: Commissioner of Food and Drugs
Date: February 5, 1979	Date: January 19, 1979

APPENDIX G

MEMORANDUM DATED DECEMBER 1, 1981, TO DR. LOWELL HARMISON, CHAIRMAN, TASK FORCE ON NCI/FDA INVESTIGATIONAL NEW DRUGS, FROM ASSOCIATE DIRECTOR FOR EXTRAMURAL RESEARCH AND TRAINING, OD (NIH), SUBJECT: "FOLLOW-UP TO NOVEMBER 23 MEETING" (REGARDING NIH ALERT SYSTEM)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date December 1, 1981

From Associate Director for Extramural Research and Training, OD

Subject Follow-up to November 23 Meeting

To Dr. Lowell Harmison, Chairman, Task Force on NCI-FDA Investigational New Drugs

In response to Ms. Porter's telephone request, I am providing additional information on topics of interest to the Task Force discussed at our November 23 meeting.

1. NIH "Alert" System

The "alert" system, as presently constituted, provides a way for NIH to track incoming grant applications and contract proposals from individuals, institutions and organizations under investigation by NIH or other Government units. The system is not intended to block the issuance of an award, but rather to provide an orderly process for the responsible NIH staff to consider any relevant investigative findings prior to making the award. We have considered modifying our central data base to automatically "block" issuance of notices of grant award for applications lacking complete documentation of assurances regarding human subjects of research. At present, however, our system does not have the absolute control over award issuance that would be required to make such a bar effective.

I am attaching our current policy and procedural guidance relating to issuance of awards during the course of an investigation. Two important points should be noted:

- The system as described herein works well for grant applications, since all competing applications must go through the Division of Research Grants (DRG) referral process. Because contract proposals may enter through 40 to 50 separate receipt points, our Division of Contracts and Grants (DCG) is developing additional guidance for R & D contracting staff to provide the necessary "alert" while protecting the privacy of offerors.
- The present process covers only new awards and competing renewals. It is clear that noncompeting continuation awards should be included, and the "alert" system will be expanded to cover those situations.

2. NIH-FDA Cooperation

We have had some very encouraging discussions with FDA dealing both with a specific case (Dr. Marc J. Straus, New York Medical College) and with general principles for cooperation. NIH and FDA staff have agreed to share information relating to their investigations of Dr. Straus and to hold joint regulatory/administrative proceedings, to the extent possible. The two agencies jointly developed a proposed DHHS initiative on misconduct in science. We have also discussed exchange of information relating to pending or completed investigations.

3. Review of Informed Consent Documents

Current NIH procedures require that awards be made only after all requirements for protection of human subjects have been met. We are about to publish revised manual issuances relating to grant and contract awards underscoring these requirements and strengthening the procedural safeguards in the review and award process. In addition, some Advisory Council members and NIH staff have raised substantive concerns about the quality of certain informed consent documents. We are currently examining ways to review some sample of those documents as an additional quality assurance. This might be approached in a variety of ways. A sample could be drawn from all applications involving human subjects, or the informed consent documents associated with every application referred to a particular initial review group could be studied. Any such review must, however, recognize the primary responsibility of the local institutional review board to assess risks and benefits and ensure that the appropriate informed consent is obtained.

I hope this information is useful. If you have additional questions please do not hesitate to contact me.

William F. Raub, Ph.D.

Attachment [Not included in Task Force Appendix for Volume II.]

Senator **HAWKINS**. The hearing in now adjourned.

[Whereupon, at 11:56 a.m., the subcommittee adjourned, subject to the call of the Chair.]

○